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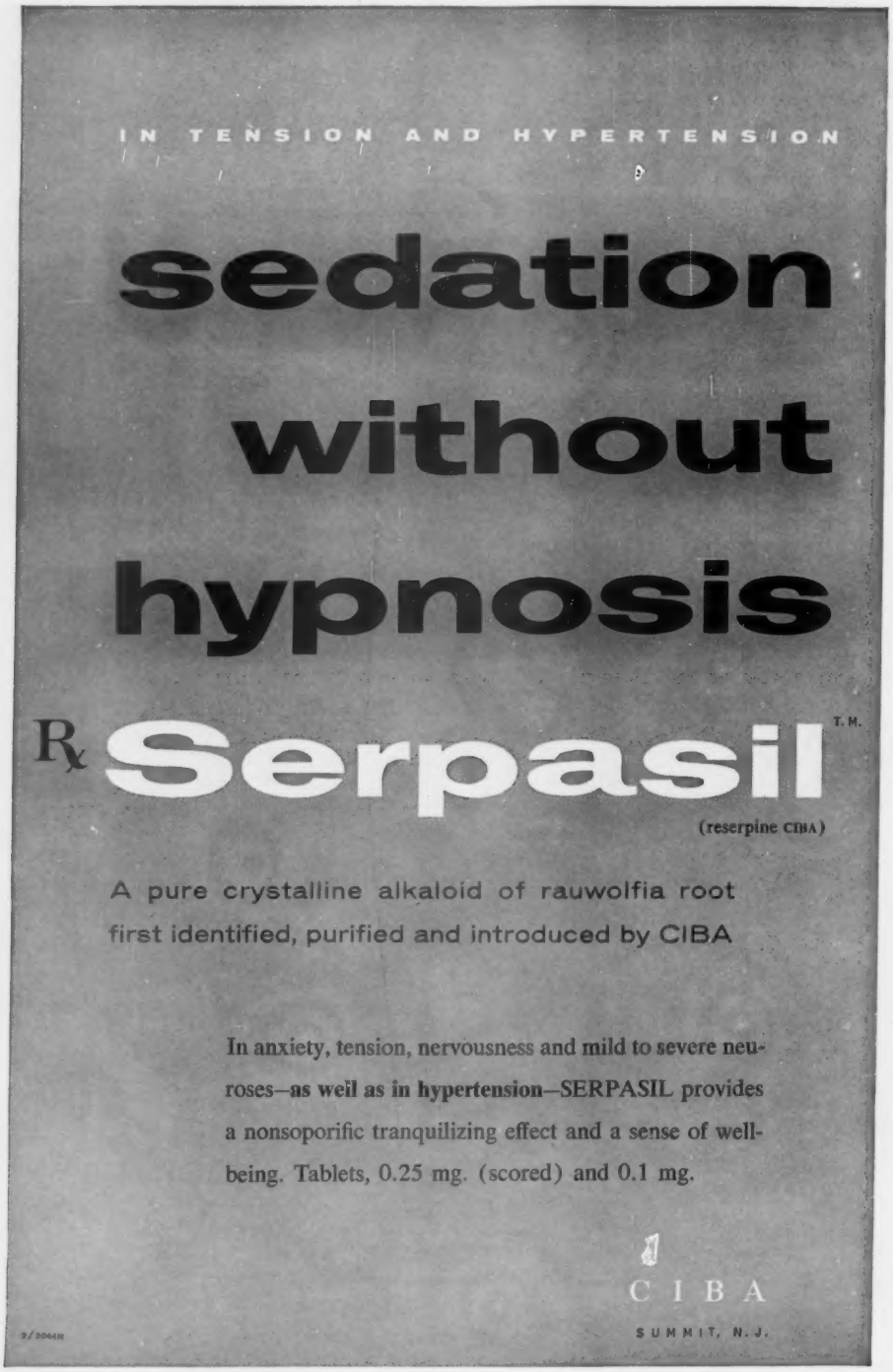
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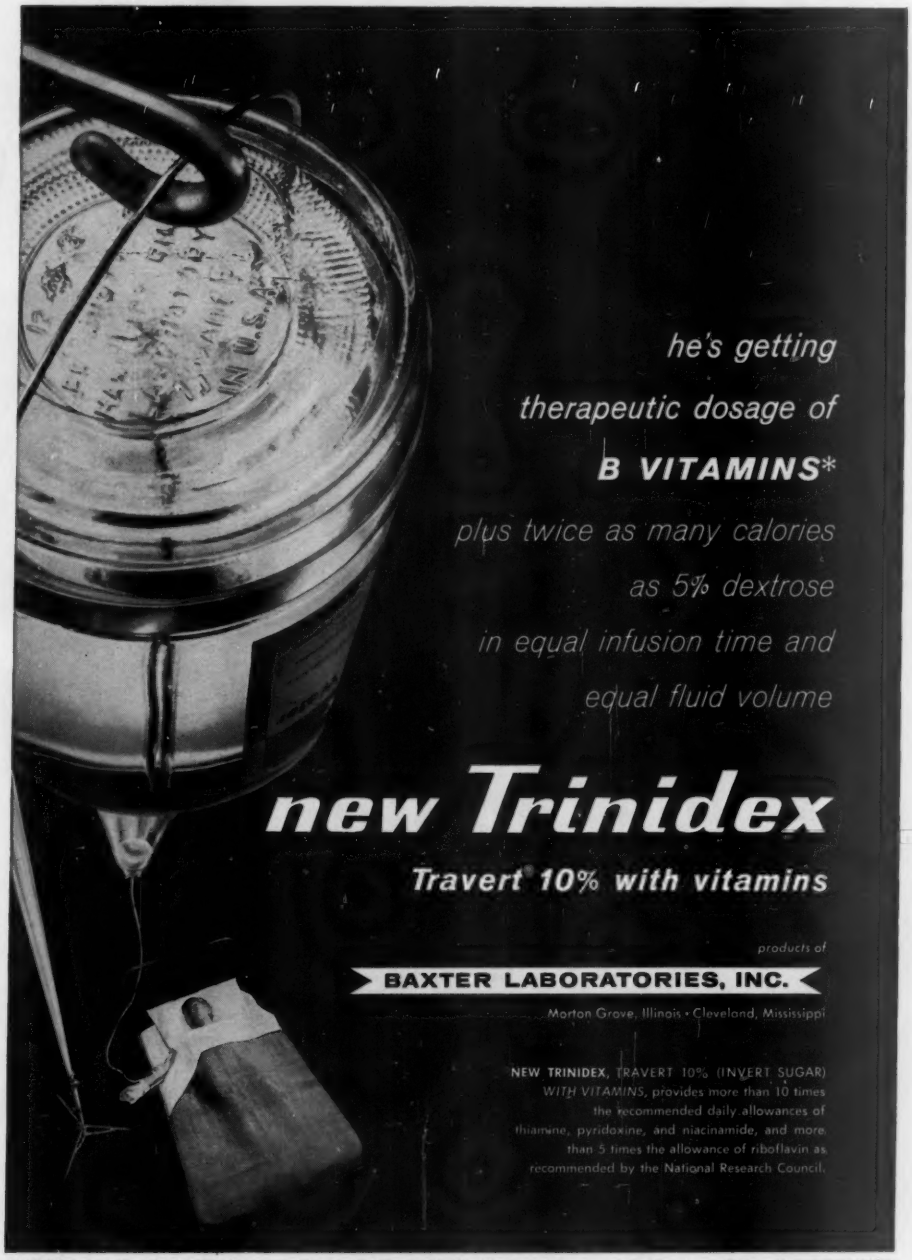
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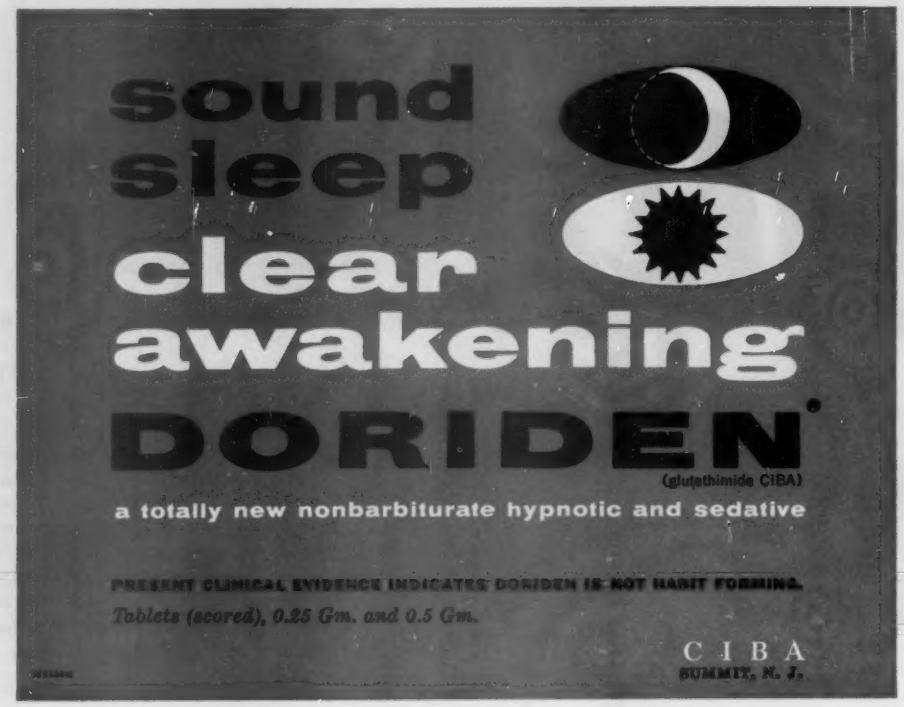

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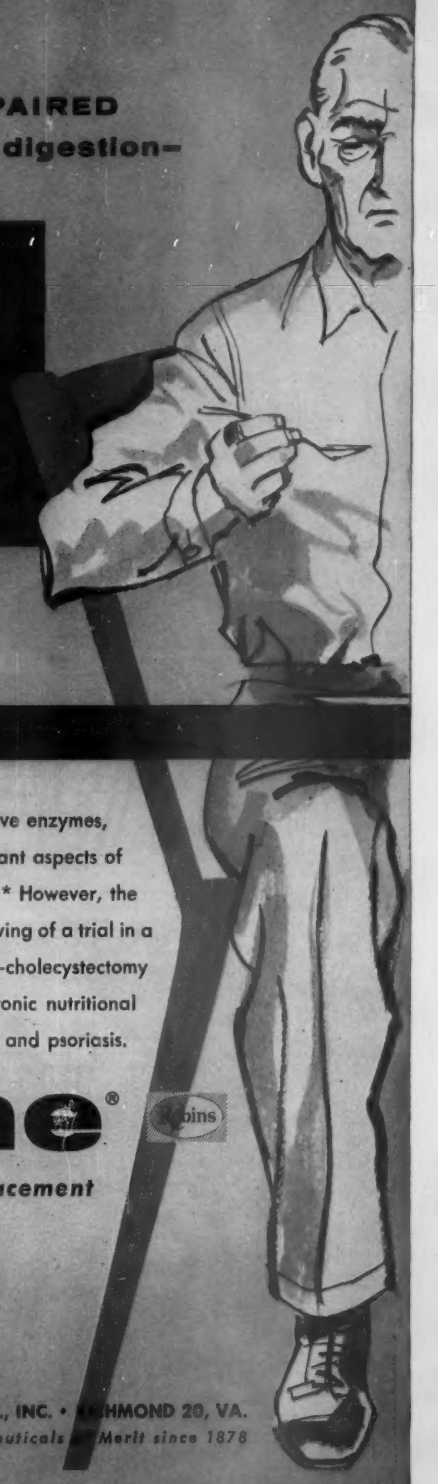

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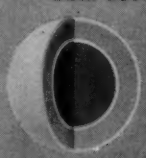

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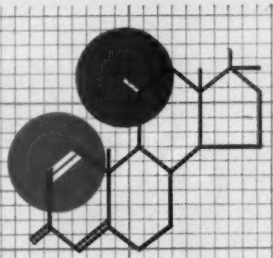

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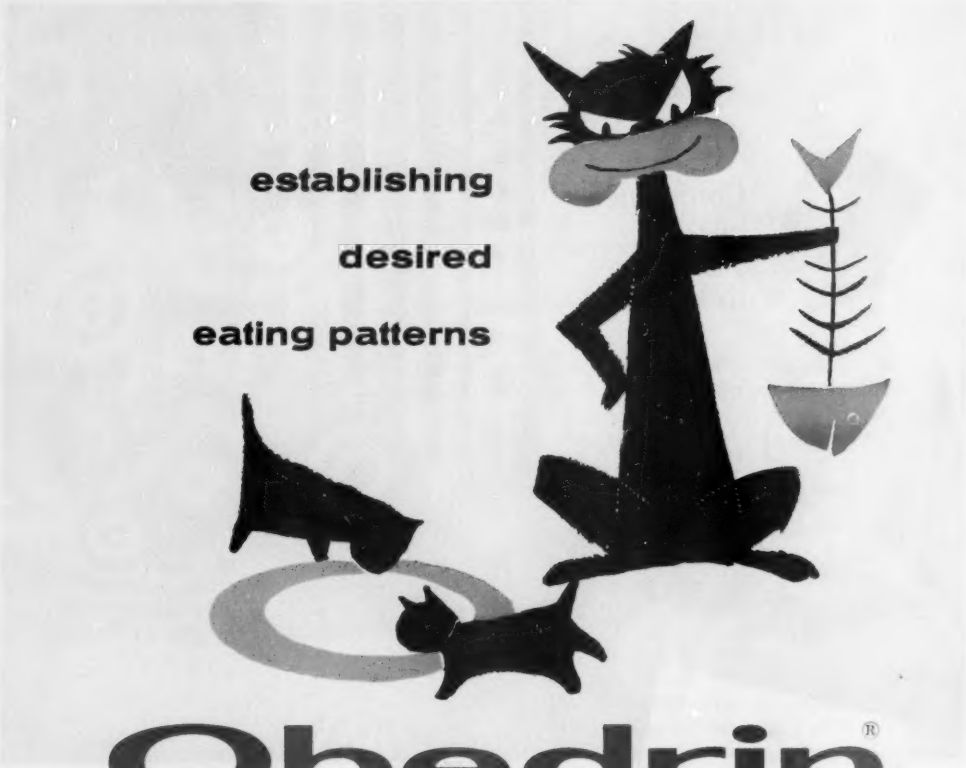

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1. Eisfelder, H. W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954.
2. Sebrell, W. H., Jr.: J.A.M.A., 152:42 (May) 1953.
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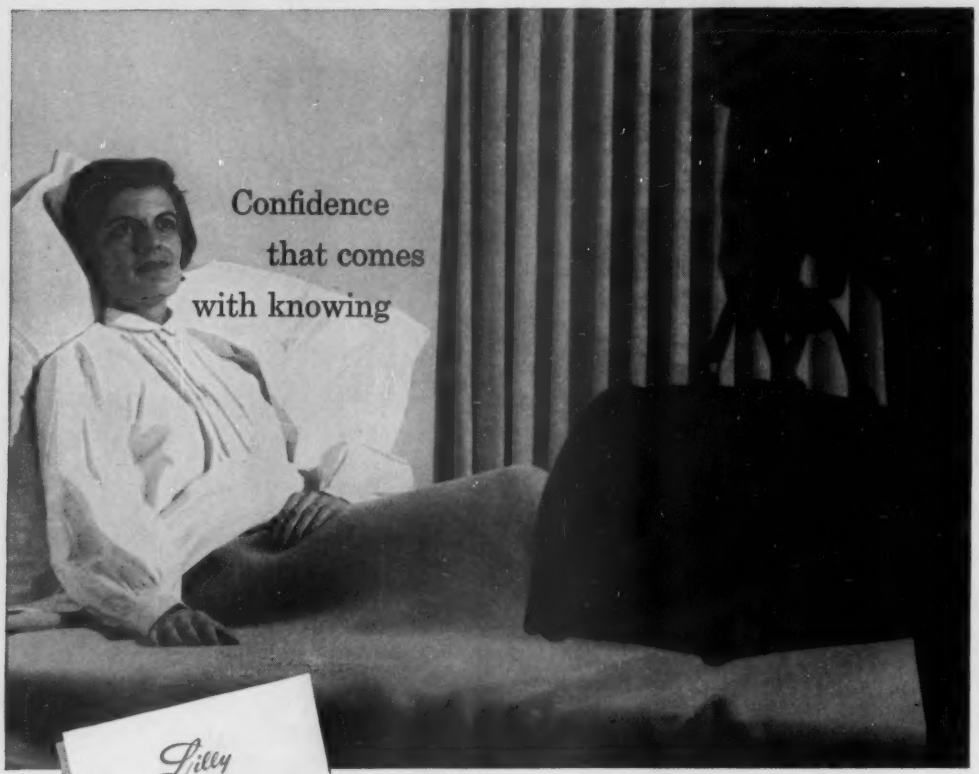

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Volume 253 AUGUST 4, 1955 Number 5

FEASIBILITY OF PARTIAL HEPATIC RESECTION UNDER HYPOTHERMIA*

WILLIAM F. BERNHARD, M.D.,† JAMES D. MCMURREY, M.D.,‡ AND GEORGE W. CURTIS, M.D.§

BOSTON

THE limiting factor in the successful surgical management of many intra-abdominal pathologic processes is the presence of hepatic involvement. Extirpation of solitary, superficial lesions of the liver is carried out occasionally, but extensive resections are as yet uncommon. Too often, the criterion of inoperability is hepatic involvement per se, rather than the extent of the process within the liver. The functional reserve and regenerative capacity of the liver cells are often disregarded in this decision. This negative attitude has been engendered by the extreme vascularity and friability of hepatic tissue.

Efforts to reduce the hazards of hemorrhage in hepatic surgery have centered around short, intermittent occlusions of the common hepatic artery and portal vein. Prolonged periods of occlusion introduce the risk of hepatic necrosis. A measure of protection for the liver is afforded by antibiotics administered during and after surgery, but this has not significantly altered the hazards of the occlusion period.[1,2]

In the experimental laboratory hepatic afferent occlusion has been successfully maintained at normal body temperature for periods of twenty minutes, but longer intervals were associated with a rapidly rising mortality rate. After an hour of occlusion this rate approached 100 per cent in a large series of animals and was not reduced by the intestinal and parenteral use of antibiotics.[3]

In the past, hypothermia has been primarily employed to permit circulatory occlusion in cardiac surgery, and interruption of the aorta for the resection of aneurysms. A marked reduction in oxygen consumption occurs during hypothermia, and thus prolonged regional ischemia of parenchymatous vital organ systems may be permitted. The present study was undertaken to ascertain the tolerance of the liver to temporary ischemia and to investigate the possibility of hepatic resection in a dry field.

*From the Surgical Service and Department of Pathology, Peter Bent Brigham Hospital, and the Laboratory for Surgical Research, Harvard Medical School.

Supported in part by a grant-in-aid from the Committee on Metabolism in Trauma, Commission on Liver Diseases, Armed Forces Epidemiological Board, and supported by the Surgeon General, Department of the Army through a contract (DA-49-007-MD-472) with Harvard Medical School. The generous assistance of the Samuel Cabot Fund is gratefully acknowledged.

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§Clinical associate in pathology, Harvard Medical School; associate pathologist, Peter Bent Brigham Hospital.

EXPERIMENTAL METHOD

Adult mongrel dogs of either sex weighing 10 to 25 kg. were used. All were fed "Kennel Bisket" ad libitum. Postoperatively, this diet was occasionally supplemented with milk and intravenous administration of dextrose and water as necessary.

The animals were anesthetized with pentobarbital sodium and intubated. Hyperventilation was carried out with a positive-pressure apparatus that maintained the venous pH between 7.40 and 7.50. Various curare preparations were utilized to control shivering. Cannulation of a femoral artery and vein was carried out, and the blood pressure in the artery measured with either a Sanborn electromanometer or a U-tube mercury manometer. Cannulation of a mesenteric vein with a polyethylene tube was performed, and portal pressures measured with a saline manometer. The level of the right atrium was estimated and used as a point of reference for these pressures. Serial electrocardiograms were also obtained.

In this experiment three groups of dogs were studied. Hypothermia was induced in two groups by means of an ice-water bath maintained at 3°C. (Table 1). Body temperature was reduced to 30-28°C., at which point the dogs were removed from the bath. The temperature drifted 3 to 5°C. and stabilized between 27 and 24°C.

Group 1 (control series, temporary hepatic ischemia in normothermic animals):

In this group of 5 dogs all were prepared preoperatively with sulfasuccidine (250 mg. per kilogram of body weight) administered for five days. This was supplemented with procaine penicillin, 300,000 units, and streptomycin, 0.5 gm. daily for two days before surgery.

After completion of the laparotomy the afferent circulation of the liver was isolated, and the vessels

occluded. The occlusions in 5 dogs varied as follows: hepatic artery and portal vein; superior mesenteric artery, hepatic artery and portal vein; inferior mesenteric artery, superior mesenteric artery, celiac axis, hepatic artery and portal vein.

Group 2 (control hypothermia series for histologic study; no hepatic afferent occlusion):

This group consisted of 8 dogs with no preoperative antibiotic therapy. Before induction of hypothermia laparotomy and liver biopsy were performed. The incision was closed, and hypothermia induced. An hour after temperature stabilization a second laparotomy was carried out, and further biopsies obtained. The abdomen was then closed, and rewarming accomplished. Biopsies were taken over a period of two weeks, and the animals killed at varying intervals up to three months after hypothermia.

TABLE 1. *Hepatic Afferent Circulatory Occlusion in Dogs of Group 1 and Group 3.*

	Mortality %	No. of Dogs	Vessels Occluded
Group 1	100	1	Hepatic artery & portal vein
		2	Hepatic artery, portal vein, celiac axis & superior mesenteric artery
		2	Hepatic artery, portal vein, celiac axis, superior mesenteric artery & inferior mesenteric artery
Group 3	7	20	Hepatic artery, portal vein, celiac axis, superior mesenteric artery & inferior mesenteric artery
		4	Hepatic artery & portal vein
		3	Hepatic artery, portal vein, celiac axis & superior mesenteric artery

Group 3 (hypothermia, with hepatic afferent occlusion for one hour—27 dogs):

Four dogs in this group had temporary occlusion of the hepatic artery and portal vein.

Three animals had occlusion of the superior mesenteric artery, celiac axis, hepatic artery and portal vein.

Twenty dogs had occlusion of the inferior mesenteric artery, superior mesenteric artery, celiac axis, hepatic artery and portal vein.

The operative procedures in all groups were carried out with an aseptic technic. Exposure of the hepatic artery was obtained by incision of the lesser omentum and the vessel isolated distal to the gastroduodenal artery. The portal vein was isolated proximal to the junction of that vein with the pancreaticoduodenal vein. Isolation of the inferior mesenteric artery, superior mesenteric artery and celiac axis was carried out at their points of origin from the aorta. All occlusions were accomplished with bull-dog clamps applied in sequence from the inferior mesenteric artery superiorly. The portal vein was occluded as the final step, thus producing complete hepatic ischemia. Liver resections were performed in some animals of Group 3.

In Group 2 liver biopsies were obtained before, during and after the period of hepatic ischemia. Specimens were placed in each of three solutions — Zenker's, 10 per cent formalin and absolute alcohol — for routine histologic study and glycogen determination.

Liver temperatures were correlated with the rectal and esophageal temperatures of some animals. These temperatures were obtained by means of an iron-constantan thermocouple mounted in an 18-gauge needle, which was inserted directly into the hepatic parenchyma. Esophageal temperatures were measured with an esophageal thermocouple, and rectal temperatures recorded by means of a mercury thermometer.

Blood cultures were obtained from the portal vein and incubated under aerobic and anaerobic conditions. In the postoperative period liver-function tests were carried out at varying intervals in Group 2 and 3.

All animals were killed at the conclusion of the experiment (one week to five months postoperatively), and complete post-mortem examinations performed.

Results

Survival Rate

In this experiment the survival rates for the normothermic and hypothermic groups differed greatly. In the normothermic control animals (Group 1), which had hepatic afferent occlusion for one hour, the mortality was 100 per cent. These animals died in a state of peripheral vascular collapse within a few hours of completion of the procedure.

In the hypothermic animals, which had occlusion of the hepatic afferent circulation for one hour, the mortality was 7 per cent (2 deaths in 27 dogs). It should be emphasized that these deaths occurred early in the series and that, at post-mortem examination, the etiology was not determined. However, no hepatic necrosis was present. In the final phase of this investigation 20 consecutive dogs survived operation and remained in good condition postoperatively.

Variations in Mean Blood Pressure

The mean blood pressure in these animals dropped 40 or 50 mm. of mercury with cooling and then stabilized. During the period of occlusion, the pressures remained unchanged and upon rewarming returned to the normal range. In the control normothermic animals blood pressures dropped precipitously when the hepatic circulation was occluded. Upon release of the occlusion the pressures remained at a low level until death.

Portal Pressure

The portal pressures before occlusion in all groups of animals ranged between 80 and 100 mm. of saline

solution. During the period of hepatic afferent occlusion, pressures varied directly with the degree of arterial occlusion to the gut. In the normothermic dogs (Group 1), one animal that had occlusion of the hepatic artery and portal vein revealed a rise in portal pressure to 600 mm. of saline solution. Two dogs with occlusion of the superior mesenteric artery, celiac axis, hepatic artery and portal vein demonstrated an increase to 400 mm. The final (2) animals of this group had portal pressures of only 170 mm. of saline solution after occlusion of the inferior mesenteric artery, superior mesenteric artery, celiac axis, hepatic artery and portal vein. The final pressures in all animals, after release of occlusion, returned to the normal range (Fig. 1).

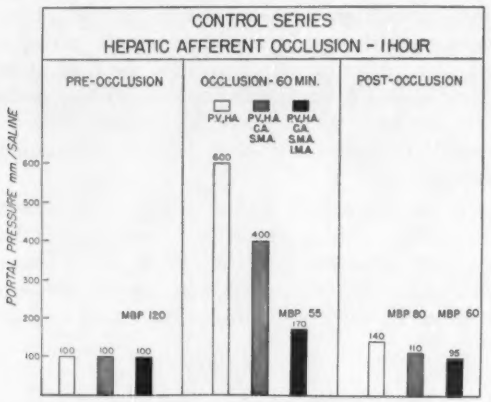

FIGURE 1. *Portal Pressures and Mean Blood Pressures for the Three Types of Operations Carried out on 5 Control Normothermic Dogs.*

During occlusion, portal pressure is highest in the dog having occlusion of the hepatic artery and portal vein and lowest in the dogs having occlusion of the inferior mesenteric artery, superior mesenteric artery, celiac axis, hepatic artery and portal vein. Mean blood pressures are low in the occlusive period and do not rise above shock levels in the postocclusive period.

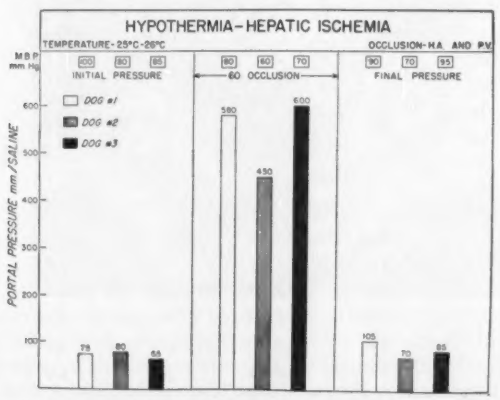

FIGURE 2. *Representative Portal Pressures and Mean Blood Pressures for 3 Dogs Having Occlusion of the Hepatic Artery and Portal Vein for an Hour under Hypothermia.*

Portal pressure drops to a normal range, and mean blood pressure rises to a normal range in the postocclusive period.

In the hypothermic animals of Group 3 (hepatic afferent circulatory occlusion) the portal-pressure relations were similar to those in the control group, but lower. In animals with occlusion only of the hepatic artery and portal vein, the preocclusion and postocclusion portal pressures were within the normal range (65 to 105 mm. of saline solution). The pressures during occlusion ranged from 450 to 600 mm. (Fig. 2). In animals with occlusion of the superior

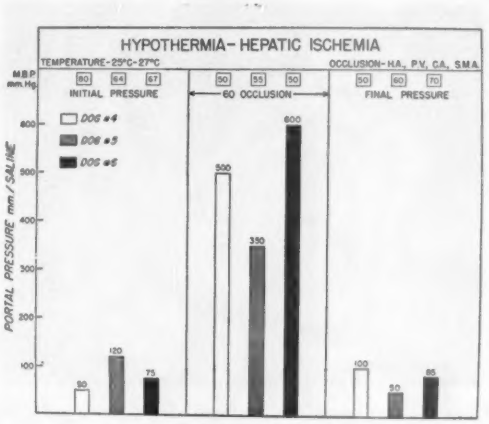

FIGURE 3. *Portal Pressures and Mean Blood Pressures for 3 Representative Dogs Having Occlusion of the Superior Mesenteric Artery, Celiac Axis, Portal Vein and Hepatic Artery. Portal pressures fall to a normal range, and mean blood pressures remain low in the postocclusive period.*

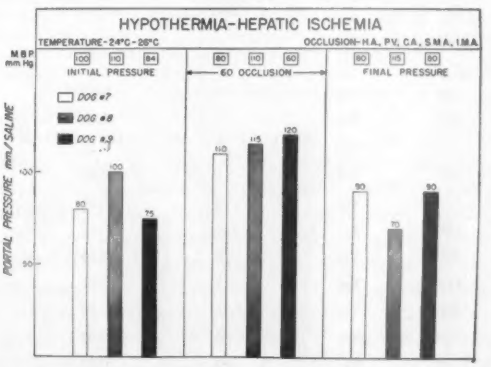

FIGURE 4. *Portal Pressures and Mean Blood Pressures in 3 Representative Dogs Undergoing Occlusion of the Inferior Mesenteric Artery, Superior Mesenteric Artery, Celiac Axis, Portal Vein and Hepatic Artery.*

There is a slight rise in portal pressure during the occlusive period, and mean blood pressures return to a normal range in the postocclusive period.

mesenteric artery, celiac axis, hepatic artery and portal vein the preocclusion pressure ranged from 50 to 120 mm. of saline solution. The pressures during occlusion ranged from 350 to 600 mm., and those after release of occlusion decreased to a range of 50 to 100 mm. of saline solution (Fig. 3). The dogs whose inferior mesenteric artery, superior mesenteric artery, celiac axis, hepatic artery and portal vein were occluded had preocclusion pressures ranging from 75 to 100 mm. of saline solution. The pressures during occlusion were 110 to 120 mm., and those after release 70 to 90 mm. of saline solution (Fig. 4).

FIGURE 5. *Mesentery and Small Bowel during Hepatic Afferent Circulatory Occlusion.*
The mesenteric cannula and manometer are arranged for measurement of portal pressure.

Appearance of Liver and Gastrointestinal Tract

In the animals of Group 1 (occlusion of the hepatic afferent circulation at normal temperature) marked cyanosis, congestion, edema of the bowel and petechial hemorrhages in the mesentery occurred. These appeared early and increased during the period of occlusion. After release of occlusion the color of the bowel improved, but edema persisted. During occlusion the liver became dark brown and remained mottled in appearance after the occluding clamps were released.

In the hypothermic dogs of Group 3 edema, cyanosis and petechial hemorrhages were present but were not so marked as in the animals of the control group (Fig. 5). With circulation restored, the color of the bowel and liver returned to normal in a minute or two.

Liver Temperatures

In all animals direct liver temperatures paralleled esophageal and rectal temperatures within 1°C.

Blood Cultures

Blood cultures taken from the portal vein of a few dogs during hypothermia grew out enterococci and *Paracolobactrum aerogenoides.*

TABLE 2. *Results of Liver-Function Studies.*

Dog No.	Occlusion	Postoperative Day	Serum Bilirubin	Bromsulfalein Retention in 45 Min.	Total Protein	Albumin-Globulin Ratio	Thymol Turbidity	Alkaline Phosphatase
			mg./100 cc.	*%*	*gm./100 cc.*		*units*	*Bodansky units*
11B	Yes	1	0.19		5.9	3.9:2.0	10	2.5
21B	Yes	1	0.18		6.5	4.1:2.4	8	4.0
	Yes	3	0.15		6.5	4.1:2.4	6	3.0
10B	Yes	1	0.23				8	
	Yes	5	0.26				16	
14B	Yes	1	0.13					
49B	Yes	8	0.15	0	6.4	4.5:1.9	1	
51B	Yes	7	0.21	5	6.8	3.7:3.1	9	3.6
52B	Yes	6	0.10	0	6.0	3.7:2.3	4	6.2
53B	Yes	5	0.08	2	6.5	4.1:214	4	3.1
9C	No	12	0.02	0	7.0	4.0:3.0	5	4.7
55B	No	1	0.10	8	5.1	4.0:1.1	8	8.6
13B	No	11	0.30				6	
	No	4	.25				8	
20B	No	3	0.15	0	6.5	4.1:2.4	8	3.0

Liver-Function Studies

Studies were carried out in 12 hypothermic dogs, 8 with hepatic afferent occlusion for an hour, and 4 without occlusion. Serial determinations over a pe-

riod of eleven days for bromsulfalein, total protein, serum bilirubin, thymol turbidity and alkaline phosphatase were within the normal range (Table 2).

Liver Biopsies and Autopsy Material

Liver biopsies on hypothermic animals with and without hepatic afferent occlusion revealed no marked alteration in liver architecture except congestion, and no residual damage as determined by routine technics was observed. Autopsies performed on these animals showed no thrombosis of the vessels occluded during operation and no abnormalities of any other viscera that could be ascribed to the hypothermia or operative technics employed. An extensive study on changes in the glycogen content of the hepatic cells is to be reported.

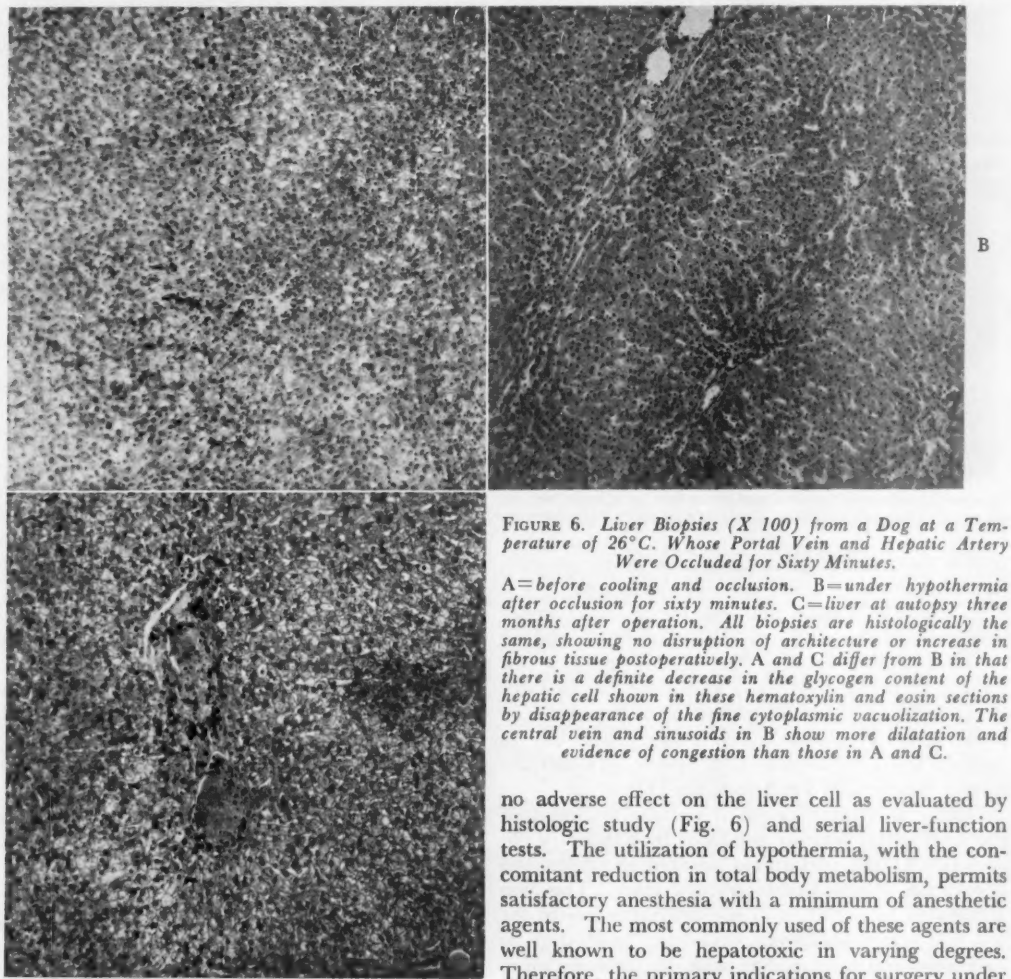

FIGURE 6. *Liver Biopsies (X 100) from a Dog at a Temperature of 26°C. Whose Portal Vein and Hepatic Artery Were Occluded for Sixty Minutes.*

A=before cooling and occlusion. B=under hypothermia after occlusion for sixty minutes. C=liver at autopsy three months after operation. All biopsies are histologically the same, showing no disruption of architecture or increase in fibrous tissue postoperatively. A and C differ from B in that there is a definite decrease in the glycogen content of the hepatic cell shown in these hematoxylin and eosin sections by disappearance of the fine cytoplasmic vacuolization. The central vein and sinusoids in B show more dilatation and evidence of congestion than those in A and C.

Discussion

In this investigation two aspects of hepatic physiology were evaluated under hypothermia: the effect of cooling on the liver parenchyma alone, and the effect of one hour of ischemia on that organ. The period of one hour was selected because, in the normothermic animal, this interval of occlusion has been found to be incompatible with survival and affords ample time for liver resection.

The data presented indicate that hypothermia has no adverse effect on the liver cell as evaluated by histologic study (Fig. 6) and serial liver-function tests. The utilization of hypothermia, with the concomitant reduction in total body metabolism, permits satisfactory anesthesia with a minimum of anesthetic agents. The most commonly used of these agents are well known to be hepatotoxic in varying degrees. Therefore, the primary indications for surgery under hypothermia should be broadened to include patients with hepatocellular disease. A classic example of this situation is the case of cirrhosis with portal hypertension and esophageal varices requiring emergency or elective surgery.

Hypotensive anesthesia has been increasingly employed for difficult surgery in poor-risk patients.[4] With this technic there is a reduction in blood flow without a simultaneous reduction in tissue metabolic requirements. This disadvantage, particularly in liver disease, does not occur with hypothermia, which also reduces systemic blood pressure. In extracardiac surgery the risk of cardiac arrhythmias is minimal,

and thus should not negate the use of hypothermia on that basis.

The lobar and segmental anatomy of the liver has been the subject of extensive investigation for many years. Application of this knowledge has awaited a technical advance to eliminate the hazard of hemorrhage, which occurs in the dissection of this friable tissue. Such an advance may be the production of regional ischemia during hypothermia.

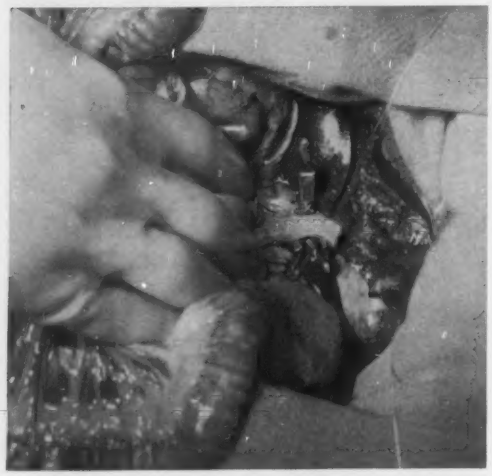

FIGURE 7. *Liver after Subtotal Resection of a Lobe during Hepatic Afferent Vascular Occlusion under Hypothermia.*

In the dog hepatic ischemia for an hour under hypothermia was carried out with survival, and no evidence of liver damage. During this period it was possible to perform extensive liver resections in a dry field. Individual suture ligations of empty vessels in portal triads were easily accomplished during the resection, and thus massive compression ligatures are largely unnecessary for hemostasis (Fig. 7).

During this investigation it became evident that the high portal pressure produced by temporary obstruction of the portal vein resulted in edema and congestion of the gastrointestinal tract. This was eliminated by occlusion of the arterial inflow to the gut just before portal-vein occlusion. In 20 dogs no adverse effects were evident with the combination of arterial and venous occlusion.

Survival in these animals with short-term afferent hepatic vascular occlusion is not dependent on collateral circulation. However, when hepatic arteries or veins are permanently obstructed, collateral vessels from the inferior phrenic arteries have been found to be significant for survival.[5] In hypothermia, necrosis of the liver is avoided by the greatly reduced metabolic requirements of this organ. Although portal-vein blood cultures in the dog are consistently positive, antibiotics before or after occlusion were not found necessary for further protection.

The clinical application of the technic of hepatic ischemia under hypothermia may be twofold. The procedure permits the resection of liver parenchyma and thereby the possible extirpation of primary or metastatic tumors. And it may permit one-stage resection of tumors in contiguous organs invading the portal vein without the hazard of a high portal pressure.

SUMMARY AND CONCLUSIONS

An investigation in dogs was carried out to determine the effect of hypothermia on liver parenchyma alone and the effect of vascular occlusion on that organ during hypothermia.

Histologic study of the liver and postoperative liver-function tests in dogs subjected to hypothermia were entirely negative.

In normothermic animals with afferent hepatic vascular occlusion for one hour the mortality was 100 per cent. Preoperative administration of antibiotics did not alter this result.

Under hypothermia, vascular occlusion of the hepatic afferent artery for one hour was carried out successfully, with only 2 deaths in twenty-seven dogs. There were no deaths in the last 20 consecutive dogs of this series. No antibiotics were administered.

Liver resection is feasible with a dry field utilizing afferent vascular occlusion in hypothermia.

It is suggested that the surgical indications for use of hypothermia be extended to include patients with hepatocellular disease requiring anesthesia and surgery, patients with primary or secondary tumors of the liver who might be successfully treated by liver resection and patients with tumor extension to the portal vein who might not otherwise be considered capable of surviving operation.

Hypothermia appears to be superior to hypotensive technics as an adjunct to the anesthetic management of patients.

We are indebted to Dr. Francis D. Moore for advice and encouragement throughout these studies and to Mr. Eugene Courtiss for his assistance in the laboratory.

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CUSHING'S DISEASE (Concluded)*

The Surgical Experience in the Care of 46 Cases

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BOSTON

NONSURGICAL TREATMENT

In the introduction we have pointed out that in our experience pituitary irradiation and testosterone have proved ineffective in bringing the disease under control. In his original papers Cushing advocated x-ray therapy to the pituitary body. It was tried in 17 patients of this series; in several of these there has been transitory subjective or objective evidence of improvement; in only one (Case 6) has sufficient physical improvement associated with changes in objective laboratory data indicated clearly that a remission followed x-ray therapy. The patient's early history has already been reported by Albright and Reinfenstein.[45]

CASE 6. An 11-year-old girl was first seen in 1942. She responded to 400 r of x-ray therapy by a slow improvement in her symptoms and signs. Regular menstrual periods returned, and there was evidence of renewed growth of lumbar vertebras on x-ray study. Five years later there was slow recurrence of symptoms and reappearance of amenorrhea. Adrenal biopsies were carried out without improvement; 3 months after 2000 more r to the pituitary gland, menses returned, and there was gradual improvement. Four years later, in 1952, her symptoms and signs recurred once more. An additional 3000 r were given to the pituitary gland without benefit. Subtotal resection of both adrenal glands was carried out in 1953, and the patient has made a dramatic, sustained response.

In spite of this failure of x-ray therapy in this series, pituitary irradiation has worked. Dr. J. C. Aub has followed one of Dr. Cushing's original patients from the beginning. He has given us the privilege of following her with him. When she was a girl of seventeen, her disease was eliminated by pituitary irradiation; she has married and has had two normal pregnancies. (She is not included in this series.)

As in other endocrine diseases spontaneous remission may occur. We have observed one such temporary remission in one of our patients (Case 11, 1945). Pituitary x-ray therapy may be sufficient to induce a remission in certain cases. Obviously, there should still be a place for pituitary irradiation in the therapy of this disease.

We have also referred to Dr. Fuller Albright's use of testosterone, estrogens, corticosterone and cortisone.[7] Twelve patients have been treated for varying lengths of time with testosterone. Although most of them responded by changing to a positive nitrogen balance and some changed from a negative to a positive calcium balance or equilibrium, in only one did a clear-cut clinical remission follow the therapeutic use of testosterone (Case 2.).

CASE 2. A 20-year-old woman, when first seen in 1935, failed to respond to x-ray therapy to the pituitary gland or to a partial adrenal resection. Testosterone was started more than one year after the last x-ray therapy and operation. A striking improvement in physical appearance and laboratory data was observed. The patient's periods resumed, positive nitrogen balance was obtained, and the 17-ketosteroids fell to normal levels. Over the ensuing 3 years there was believed to be no further progress of Cushing's syndrome. Ultimately, however, she died of the effects of renal stones and bilateral renal sepsis initiated by the pathologic process. There was a difference of opinion about the activity of the Cushing's disease. She died at home without autopsy.

The testosterone therapy improved the clinical well-being of some of the patients, perhaps by improving muscular strength. The respite was short lived, and the Cushing's disease marched on. Because of its beneficial metabolic effects, testosterone may still prove to be an important adjunct to therapy.

The negative potassium balance and the occasional low serum potassium level can be reversed to normal conditions by the administration of potassium chloride by mouth. Under this therapy the symptoms and signs of the disease that are associated with the abnormalities in potassium metabolism disappear or improve, and the patients often have a significant subjective improvement. There is no effect, however, on the fundamental course of the disease.

The use of these nonsurgical measures is to be restricted to patients in whom the pathologic type of adrenal disease is known to be hyperplasia. If a tumor is present, surgical treatment is mandatory.

SURGICAL TREATMENT

Aims

The aims of surgical treatment are to reduce the secretory activity of the adrenal cortices to within normal limits and to remove any neoplastic tissue that may be present. When a hyperfunctioning neoplasm is the cause of the syndrome both aims are accomplished by excision of the neoplasm; the undiseased tissue in the opposite adrenal gland remains to resume and carry on normal hormonal function. The surgical problem is defined and straightforward. When hyperplasia of both adrenal cortices is the etiologic anatomic type, the problem is more complicated. In general both glands have to be exposed, and the greater portion resected. Just how much to resect cannot as yet be arbitrarily defined, and we

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have become confident in our judgment only with increasing experience.

Preoperative Diagnosis or Exclusion of Tumor

The operative management is facilitated if the surgeon knows beforehand the pathologic type of adrenal disease with which he must deal. In only 2 cases was the tumor large enough to be appreciated on physical examination. Both were patients with a malignant tumor (Cases 4 and 32). Pain on the side of the tumor is too late a symptom to be relied upon. It was present in only one patient and was presumably due to the spread of the malignant process (Case 1). Differential analysis of the urinary hormone pattern has not provided an adequate distinction between tumor and hyperplasia. On the other hand duration of the disease may be helpful; our patients with tumor have on the average had a shorter history. It must be emphasized, however, that roentgenographic study has been the most successful means of differentiation.

Tumors 5 cm. or more in diameter were readily recognized by a plain roentgenogram. The 2 largest tumors displaced the neighboring organs, principally the kidney, leaving no doubt of their presence and posterior position. The visualization of a small tumor or bilateral hyperplasia has been more problematic.

We have found the normal or slightly enlarged adrenal gland difficult to demonstrate by roentgenogram even under the most advantageous conditions of body build and bowel preparation. After the gastrointestinal tract has been emptied of gas and feces, the normal adrenal gland can be seen in a thin person as a triangular shadow above either kidney. In an obese person the shadow may be blotted out by the other body tissues since its density is slight, scarcely more than that of fat.

Periadrenal air insufflation has been carried out in 18 of our cases. To avoid air embolism the air was injected below the kidney.[46] In our initial experience we thought this method of visualization gratifying, but in our more recent cases we have realized that the well taken plain film after proper preparation offers as much.*

Our current practice is to take simple plain films at somewhat different angles in the anteroposterior position. A small shadow on either side scarcely visible is consistent with a normal gland. If the density and size are slightly greater than the expected normal for the body build of the patient and if the shadows are approximately equal a diagnosis of bilateral hyperplasia is justifiable. If one gland is denser and larger than the other in different positions and on repeated examination, a neoplasm is presumed.

Intravenous or retrograde pyelograms offer little diagnostic help regarding the presence of a small adrenal tumor or bilateral hyperplasia. The intravenous pyelogram sharpens the outline of the upper pole of the kidney by increasing the opacity of the kidney, but ordinarily the upper pole of the kidney is readily visualized on the plain roentgenogram. Large tumors in displacing the kidneys may blunt the upper calyces, but such evidence of renal distortion is not needed to make a diagnosis of the presence of a large adrenal tumor. Neither displacement nor distortion of the kidney occurs from hyperplasia or a small adenoma.

A small adenoma has been more readily visualized in the left than in the right adrenal gland. This we believe is due to the presence of the liver on the right side. In 3 of our patients with small adrenal adenomas the adenoma was partially buried in a rounded concavity of the right lobe of the liver. Although it was suspected, a definite diagnosis of an adrenal neoplasm was not made in these cases preoperatively.

Operative Management

Operative approaches to the adrenal gland. The adrenal glands may be approached surgically by a variety of ways: transabdominally, transthoracically or retroperitoneally. In our earliest operations the gland was approached through a paradorsal longitudinal incision over the lateral border of the sacral spinalis muscle from the eleventh rib to the sacrum. This approach was much like the incision of Young[48] except that we avoided pulling on the adrenal gland by dividing the eleventh and twelfth ribs and retracting the diaphragm upward. Seven of the patients with Cushing's disease were operated on in this way. In none of these were both glands approached at the same operation by the bilateral incisions recommended by Young. Experience with 4 patients with adrenal virilism suggested that the surgical procedure was too extensive. This approach gives better access to the adrenal gland than the subcostal incision frequently used to approach the kidney. It has been abandoned as less satisfactory than the extrapleural transdiaphragmatic approach described below.

Dissatisfaction with the paradorsal approach soon led to exploration of the transthoracic route. Incision can be made through the bed of either the ninth or the tenth rib, opening into the pleural cavity and dividing the diaphragm immediately above the adrenal gland. This is a good approach, but the line of incision and maximum exposure is now above the gland. The distance to the lower part of the gland and to the pedicle of the kidney is too great. The fact that the paradorsal approach was too far below and the transthoracic approach was too high above the gland, led us to realize that the most direct and easiest route would be through the bed of the eleventh rib. Therefore, the subpleural transdiaphragmatic operation was developed.

*Recently, reports have appeared from Spain and from San Francisco recommending retroperitoneal air injection as a means of visualizing the adrenal glands.[47] Some of the photographs are impressive, but the authors have been dealing with large tumors, which we suspect could equally well have been visualized by plain roentgenograms after adequate intestinal preparation.

The subpleural transdiaphragmatic approach gives by all odds the best visualization of the gland, the most ready access to the diffuse blood supply and the best opportunity to resect metastatic spread if the tumor is malignant. If wider exposure is necessary, the incision may be extended easily by opening the peritoneal cavity anteriorly or by opening the pleural cavity superiorly. Incision is made over the entire length of the eleventh rib. The rib is excised subperiosteally, care being taken not to open the pleura. The inferior reflexion of the pleura, which crosses transversely at the midportion of the eleventh rib, is then visualized. The diaphragm is opened at the outer end of the eleventh rib and sectioned from lateral to medial about 1 cm. below the pleural reflexion. It is divided nearly to its crus, to a point under cover of the sacrospinalis muscle. The aperture is widened by a mechanical retractor placed between the tenth and twelfth ribs. The sacrospinalis muscle and the undivided medial portion of the diaphragm are retracted with a hand retractor, giving wide exposure of the perirenal fascia. This fascia is then opened, exposing the perirenal fat. Without separating this fat from the kidney, the kidney is depressed downward by the assistant's hand, and the adrenal gland is found above the kidney in the vault of the perirenal space.

A succession of technical steps at this juncture in the operation have been found useful in facilitating exposure of the adrenal gland and early appraisal of the pathologic type of the disease. The normal gland in the healthy person floats in a generous deposit of fat above the upper pole of the kidney. In many patients with Cushing's disease this fat deposit is increased and identification is more troublesome. Held by its vascular supply from the inferior phrenic vessels, the adrenal gland generally lies in the fornix of the perirenal space. It is best to expose first the surfaces of this fornix, retracting the gland down by its attachment to the kidney. If the inferior surface of the adrenal gland is first exposed by dividing the fatty plane between it and the kidney, the means of retracting the gland downward will have been sacrificed. When the blood supply from the inferior phrenic vessels has been divided and the adrenal gland is retracted downward into the center of the exposure, its middle blood supply direct from the aorta and to the vena cava and the inferior blood supply from the renal pedicle can be readily isolated. The inferior surface of the adrenal gland over the kidney is the last to be exposed.

The paradorsal, transthoracic and extrapleural transdiaphragmatic approaches all share the disadvantage that only one gland can be exposed by a single incision. This is not a disadvantage if the patient's disease is due to an adenoma or carcinoma since only the adrenal gland containing the neoplasm need be exposed. If the side selected for the first exploration proves to contain an atrophic rather than a neoplastic gland, or if the disease process is bilateral hyperplasia in which both adrenal glands must be subtotally resected, two incisions are necessary.

The desirability of avoiding a two-stage procedure has demanded consideration of the transabdominal approach since it is the only approach by which both adrenal glands can be visualized through a single incision. A broad transverse incision across the upper abdomen has been used in 6 cases (the one infant and 5 others). All these patients were thin enough to permit exposure of the adrenal glands. The transabdominal route is not to be recommended for patients with an obese abdomen.

Subtotal resection. Relief of the disease in the patient with the hyperplastic type demands either radical subtotal or total excision of both adrenal glands. Certain clinics are practicing total removal of both adrenal cortices.[49,50] We suppose that this practice has developed because of the difficulty of achieving complete and permanent relief by subtotal resection. In our first 2 patients with hyperplasia of the adrenal cortices and Cushing's disease our tentative attempts at resection failed to be followed by improvement and a few of our later patients obtained only temporary or partial relief so that secondary operations were required. In spite of this we cannot agree with the policy of total resection. The amount of the adrenal hormones needed varies so acutely in the ordinary stresses of life that we believe that a young person like those who so commonly have this disease needs a remnant of cortical tissue that can respond to an abrupt increase in need. Total dependence on substitution therapy with cortisone in our present state of knowledge seems hazardous, and total resection condemns the patient, therefore, to a life of jeopardy. Since subtotal resection, if carried out radically, does achieve relief of the disease and apparently permanently so, it seems the method of choice.

The principle of subtotal resection is the same as that which has been employed for so long in hyperthyroidism and more recently in hyperparathyroidism. The degree of resection demanded, however, appears to be quantitatively more extreme than that in hyperthyroidism.

Consistent success in the relief of Cushing's disease has been achieved when at least 90 to 95 per cent of the adrenocortical tissue has been resected. The removal of less than half the cortical tissue on both sides in our first 2 patients (Cases 2 and 3) did not objectively affect the course of the disease. In a third patient the removal of 30 per cent of one adrenal gland only brought about a remission, but the patient has subsequently had a mild recrudescence (Case 14). The resection of 60 per cent of both adrenal glands in Case 13 brought relief, but there has been a subsequent recurrence, necessitating another operation.[51] All these patients were operated on when desoxycorticosterone acetate and adrenocortical extract were the only two specific cortical therapies available; these were known at that time to be inadequate.

With the advent of cortisone, a more potent and accountable cortical therapy, we have practiced a considerably more radical subtotal resection, removing at least 90 and often 95 per cent of both adrenal glands. In only one patient so treated has there been recurrence thus far (Case 34). The majority have had a subtotal resection of both glands in two stages. In 3 recent cases simultaneous bilateral subtotal resections have been carried out through the transabdominal approach. It is in one of these last that a recurrence has been manifest, and the remnant of the right adrenal gland has subsequently been resected. The remnant appeared to have doubled in size since the previous resection a year earlier. Presumably, the remnant on the right side has similarly doubled.

It is not known at this time to what extent the remnant of the adrenal cortex is able to regenerate after a subtotal resection. In experiments with rats it has been found that essentially an entire gland will regrow from the capsule.[52,53] The normal gland in the human being may have a comparable regenerative power. In one of our patients who died several months after total adrenalectomy for cancer of the breast, autopsy disclosed two hyperplastic nodules not observed at operation. If a hyperplastic remnant could increase in like measure this would be an additional indication for radical subtotal resections in patients with Cushing's disease.

Case reports. Experience with the cases reported below emphasizes the problems attending successful resection of the hyperplastic adrenal cortices. Case 16 illustrates the limited effect of partial adrenalectomy and the need for radical excision. Case 44 demonstrates that early radical subtotal resection is followed by prompt and effective relief.

CASE 16. A 42-year-old woman was referred in 1946 with a diagnosis of Cushing's disease already established. The disease had started 6 years earlier, and 3 years before coming to us she had received x-ray treatment to the pituitary gland without recognizable effect. She had the classic appearance of extreme Cushing's disease; she was hypertensive and amenorrheic. Perirenal-air-insufflation roentgenograms gave no evidence of tumor. The left adrenal gland was exposed by the paradorsal approach; it was consistent with hyperplasia. Forty per cent of it was removed.

The patient's periods returned and continued regularly every month. She was sufficiently satisfied that she refused to have the other adrenal gland operated upon at that time. By 1950 she had become weaker and agreed to a second surgical attempt. On March 9, 1951, the entire right adrenal gland was removed through the transdiaphragmatic extrapleural approach.

There was some return of strength in the succeeding 2 years. Then, the hypertension was found to have increased, and the patient suffered 2 episodes of cardiac insufficiency. She returned in May, 1953, for a 3d surgical attack. The remnant of the hyperplastic left adrenal gland was radically resected, leaving approximately 1 gm. of tissue.

After this resection improvement has been dramatic. There has been a weight loss of 40 pounds, with loss of the fatty habitus, a gain in strength and a feeling of well being, a decrease in hypertension and disappearance of ankle edema. The patient, family and friends have been amazed and delighted with the seeming deliverance.

Two years after operation she is still needing 20 mg. of cortisone daily to maintain her feeling of well-being.

CASE 44. A 33-year-old man came to us in October, 1953. Nervousness, fatigue, muscle weakness, the abnormal adiposity, acne, and a flushed face had developed within 9 months. He had become so weak that he had to pull himself upstairs with his hands. Sexual potency had disappeared. Roentgenograms gave no evidence of tumor. On October 14 the right adrenal gland was exposed through the transdiaphragmatic extrapleural approach and was found to be hyperplastic. Ninety per cent of the gland was resected. On October 23 the left adrenal gland was similarly exposed, and the same proportion resected. Cortisone was gradually withdrawn during the succeeding 6 months, during which the skin peeled and thickened with disappearance of the acne. The ruddiness of the face has disappeared with loss of the abnormal obesity. Strength has gradually returned with growth of the muscles to their previous size. Sexual potency has returned. One year after operation the patient considered himself physically rehabilitated. This status has been maintained through the second year.

Tumor resection. The surgical problem presented by a tumor is simpler in principle than that presented by adrenal hyperplasia. There may be difficulty in achieving a total resection of the tumor, particularly if it is malignant, but the endocrine problem is simpler. All the hyperfunctioning tissue is contained within the tumor. The tumor must be resected totally and intact. If there is malignant spread it too must be resected. The uninvolved tissue is left behind to be reactivated and to carry on the normal endocrine function. The undiseased atrophic adrenal tissue of the opposite gland is always available. If the tumor is a small one and has developed in one pole of the gland there may in addition be the remaining atrophic tissue of the same gland. If the atrophic portion can be left behind without endangering total resection of the tumor, in our opinion this should be done. This was possible in 7 of the 10 benign adenomas resected.

In our first patient from whom a malignant tumor was removed (1938) a portion of the tumor was left behind because of the extreme degree of atrophy proved by previous operation in the gland on the other side. Such subtotal resection would not now be practiced in view of the availability of cortisone. In the other 2 operable malignant tumors the entire adrenal gland was resected.

Preoperative Preparation

The aspects of preoperative preparation specific to the patient with Cushing's disease relate to postadrenalectomy cortical insufficiency and to a presumed cellular deficiency of acute healing. Both these aspects are dealt with in detail in the section below on the postoperative management. They are now best covered by the preoperative and intraoperative administration of cortisone and require no other specific therapy. We have not judged successful the efforts to anticipate the postoperative nutritional needs by stuffing the patient before the operation with nitrogen and potassium. Even with simultaneous administration of testosterone we doubt if significant quantities of tissue have been rebuilt during the active phase of the hyperfunctioning cortex. Potassium has been effective in eradicating hypokalemia, however.

It has been our practice in the last four years to give 100 mg. of cortisone intramuscularly twelve hours before operation and again immediately before the start of anesthesia. It is possible that in the future we shall prefer the intravenous administration of compound F during operation.

Anesthesia

Nitrous oxide, oxygen and ether and cyclopropane have been used as anesthetic agents. We have no preference. At first we avoided cyclopropane because of the occasional increase in bleeding in the operative site. This we have not found to be of moment in these patients in spite of the fragility of the tissues. Because of the possible opening of the pleural cavity the anesthetic has always been administered with an intratracheal tube and preparation for positive pressure.

Postoperative Management

The postoperative care specific to the patient with Cushing's disease includes buffering both an acute cortical insufficiency and what we presume to be an acute nutritional deficiency. The acute cortical insufficiency is created by the resection of the adrenocortical tissue, leaving either atrophic tissue or an amount of hyperplastic tissue inadequate for the immediate needs. It is short-lived and readily met with cortisone. At the beginning of operation the patient has an excess of the adrenocortical hormones; the normal response to operation is now believed to demand extra cortical hormone. In keeping with this concept the patient with Cushing's disease in whom no adrenocortical tissue is resected sails through operation unhampered. In our patients in whom exploration has revealed only atrophic tissue, indicating a tumor on the other side, it has not been necessary to give any supplementary cortisone. This smooth response contrasts with that to the second operation at which the tumor is resected. Likewise, in the patients in whom one hyperplastic adrenal gland has been subtotally resected, we have found it unnecessary to give any supplementary cortisone postoperatively; they have done well. At the second operation, however, when the second hyperplastic gland is subtotally resected, the remaining cortical tissue is inadequate to secrete the excess of hormone needed to carry the patient through the immediate postoperative period.

In our early cases, even with large doses of adrenocortical extract, desoxycorticosterone acetate and salt, there were indications of acute cortical insufficiency such as low blood pressure and fever coming on within four to twelve hours after operation. In our last 20 cases we have given each adult patient 300 mg. of cortisone in the first twenty-four hours and for each of the next twenty-four hours until the postoperative course is assuredly smooth. By the second to the fourth day the dose of cortisone is tapered off, 50 mg. less being given each day. In the patients with a tumor and a contralateral atrophic adrenal gland we have found it possible to reduce the dosage of cortisone to the neighborhood of 50 mg. by the tenth day to the fourteenth day, when the phase of acute cortical insufficiency seems to be passed. At this time the phase of acute cortical insufficiency has yielded to that of the nutritional deficiency, and further cortisone is given to moderate the latter condition.

ACTH has not been tried in the postoperative therapy of patients with hyperplastic adrenal glands since there may not be sufficient adrenocortical tissue left for it to act upon and also since there is presumably a continued overactivity of the anterior pituitary body with an adequate amount of the patient's own ACTH. In the postoperative therapy of patients who have had a tumor removed we have preferred to permit the atrophic adrenal tissue to respond to stimulation from the patient's own pituitary gland without additional ACTH.

After the surgical correction of adrenocortical hyperfunction there is a stormy reaction, which we believe is related to the rapid rebuilding of tissues and which we are calling the acute nutritional-deficiency phase of healing. This phase is a most disagreeable one for the patient, can be lethal if not adequately treated and demands prompt care. It is closely related to the result of surgical therapy as the evidences of the disease disappear, but it is so important a consideration during the postoperative management that it is discussed here rather than under therapeutic results.

This phase first came to our attention after the resection of two adenomas in Case 9 in 1944. For the first few days the patient apparently was doing well; then she became restless and complaining and gradually slipped into coma. On the tenth day the kidneys stopped secreting, and yet by the fourteenth day, when she died, there had been no elevation of the nonprotein nitrogen. The potassium level of the blood was low. There were two suggested conclusions: one was that adrenal insufficiency resulted in water retention and the second was that she had not been fed sufficient cellular elements to meet an acute need. Four months later we were confronted by the same situation (Case 10). The patient was given vigorous intravenous alimentation with amino acids and intracellular electrolytes. Although her convalescence was stormy she slowly recovered. Since that time the metabolic balance of several of our patients has been observed. Although a positive balance of nitrogen and other cellular elements has been quantitatively demonstrated in only 1 patient,[42] we are reasonably certain that the effectively adrenalectomized patient with Cushing's disease promptly passes into a positive cellular balance and that the stormy symptoms are related to the regrowth of tissue and consequent nutritional needs.

The concept of the phase of nutritional repletion was suggested by our earlier experience with the

tetany of recalcification in patients with hyperparathyroidism corrected by resection of a parathyroid tumor.[54] In these patients there is an acute and short-lived phase of parathyroid insufficiency. In patients with severe bone depletion before operation there is a prolonged and severe tetany and need for calcium. This tetany can be met only by huge doses of calcium, and it fades only as bones are replenished and healed. The comparison with Cushing's disease is an obvious one because the gastrointestinal symptoms, the bone aches and the skin trouble disappear as the skin returns to normal, the muscles enlarge, strength returns, the abnormal adiposity disappears and the feeling of well-being returns.

The symptoms of the stormy phase of acute nutritional deficiency are nausea, bone and joint aches, dermatitis and, in some patients, an intensification of anxiety. The nausea in a number of our patients has been pronounced, making it difficult to meet the primary difficulty. Intravenous alimentation therefore became doubly important. The nausea may start in the first days and may be so intense that the patient refuses to eat. In a patient with a severe degree of the disease it may last for several weeks to months. Fortunately, the nausea can be tempered successfully by cortisone. If nausea appears as the cortisone is diminished in the first two postoperative weeks we have found it helpful either to hold the dose of cortisone steady or to raise it slightly. When appetite returns we slowly decrease the cortisone until the nausea reappears. The appearance of nausea in this manner has been a useful indicator of the best cortisone level.

Bone and joint aches have been stubborn symptoms for several months in patients with severe osteoporosis. They have been mild in other patients with little osteoporosis. We believe — but do not know — that they are related to recalcification of the bones and to changes in periarticular soft tissues. We have not delayed the tapering off of the cortisone on this account, but we have not found any specific therapy effective. It has been our policy to provide a generous amount of calcium, phosphorus and magnesium in the diet.

Peeling skin, itching and dermatitis have been common among our patients in the postoperative phase. Starting at the end of the first postoperative week virtually all our patients have peeled much as though they had had a sunburn. The peeling may persist for six to eight months. Gradually, as the skin thickens and softens, the peeling vanishes. An intense itching of the skin and a mild eruptive dermatitis have been encountered in about 20 per cent of our patients. This too disappears gradually with healing of the skin. If it becomes too severe it may be ameliorated by an increase in the cortisone dosage. A severe dermatitis plagued 2 of our patients for the first eight weeks after operation.

Four patients have become deeply tanned on exposure to sunlight during the first two years after operation. Bluing of the tongue occurred in 2. All 4 had had an otherwise successful subtotal resection of hyperplastic glands. In view of this experience, it is our policy now to warn patients about exposing themselves unduly to sunlight during this phase of their recovery. The pigmentation is doubtless related to but not identical in origin with that occurring in Addison's disease; the patients were well and free of symptoms of hypocortinism at the time they were exposed to the sun and became pigmented.

The prolonged phase of nutritional replenishment has been accompanied in many of our patients by a feeling of uneasiness and uncertainty. In those with severe anxiety before operation there has been an exacerbation of the anxiety in the initial postoperative week. Only as healing becomes obvious are they reassured. The anxiety appears to parallel the gastrointestinal discomfort and is ameliorated when acute by a slightly higher cortisone dosage. As healing nears completion we have been amazed to see the changes in personality as the anxiety fades.

Detailing the actual cortisone dosage employed in the various patients gives an inadequate picture of the difficulty of the management of this phase of Cushing's disease. It has been possible to reduce the cortisone to 40 mg. a day in almost all patients by the third week after the effective operation. In some patients it has been omitted by the end of the third month. In some of the more severe cases the cortisone has gradually been tapered off but not omitted until a year or even longer has passed. In some patients the cortisone has been kept at a low dosage of 10 to 15 mg. a day more, with the idea of helping to control excessive anterior pituitary activity rather than to continue to temper the rate of nutritional repletion.

Results

After successful operative relief of hyperadrenocorticism the manifestations of Cushing's syndrome are reversed. This process produces so striking an alteration in appearance that members of our staff who have not followed the patients closely after operation have not recognized them after complete recovery. The process is gradual, and it may take six months to a year or even longer to reach its end. The abnormal fat deposits vanish; the face loses its ruddy appearance and becomes slender; the abnormal body hair is shed; as the skin peels and thickens, the striae fade; acne disappears; easy bruising ceases; the muscles become firmer and of normal bulk as strength returns; the blood pressure usually falls to normal. The laboratory findings are reversed. X-ray films of the bones give evidence of calcium deposition.

In patients with disease of long duration, however, there may be residual abnormalities. A significant degree of hypertension has persisted in 3 of our patients, and we suspect that irreversible damage to arterioles had developed. Signs of arterial insufficiency persisted in 1 patient, thirty-three years of age, with chronic leg ulcerations; the ulcers did not heal until five years after the operation (Case 20). The renal stones and

kidney infections initiated during the active phase of Cushing's syndrome created special problems in 2 patients after the original disease was cared for. One passed a stone, and the other died of renal infection.

The evaluation of results of surgical therapy requires division of the cases into those with tumor and those with adrenal hyperplasia. To judge the adequacy of the excision of hyperplastic tissue, it is also essential to subdivide the patients further, separating those who were operated on during the period of faltering understanding and inadequate hormone therapy from those operated on since the advent of cortisone, when radical resection has been safe. The results are summarized in Tables 4 and 5.

Malignant Adrenocortical Tumors

The results of surgical extirpation of malignant tumors of the adrenal cortex associated with active Cushing's syndrome have been discouraging because the tumors had already metastasized widely by the time the patients were explored. Two patients died with active Cushing's syndrome and metastatic malignant tumors before exploration could be carried out (Cases 1 and 7). One was considered inoperable when the adrenal gland was explored (Case 32). Two malignant tumors were resected. Of these 2 patients (Cases 4 and 37) 1 died within a year of widespread metastatic disease and active Cushing's syndrome. The second died one day after the operation. At autopsy an embolus was discovered in a subdivision of one pulmonary artery, but in retrospect we now believe that adrenocortical insufficiency played a major part in her death.

TABLE 4. *Operative Results in 12 Patients with Benign Adenoma.*

OPERATION	NO. OF CASES	RESULT			
		PATIENTS WHO DIED WITH ACTIVE DISEASE	PATIENTS WHO DIED WITHOUT ACTIVE DISEASE	PATIENTS LIVING WITH ACTIVE DISEASE	PATIENTS LIVING & RELIEVED OF DISEASE
None	1	1	0	0	0
Resection	11	0	1	0	10

Benign Tumors

Only one patient with a benign tumor of the adrenal cortex associated with Cushing's syndrome died before the tumor was removed (Case 22). This patient died as a result of acute cholecystitis complicating severe Cushing's disease. Of the 11 patients whose benign tumors were totally resected 10 are living and apparently cured from nine months to ten years after operation. None of these patients require maintenance on cortisone therapy. The other patient died two weeks after operation in the phase of nutritional deficiency and hypocorticism described above. (Table 4).

Hyperplasia

Of the 27 patients with hyperplasia of the adrenal cortices 2 had no operation, and the pathologic type was disclosed by autopsy. The entire surgical care of 7 was carried out before cortisone was available. The initial operations of the next 6 were before cortisone, and the final operations were with the aid of cortisone. The remaining 12 have been operated on wholly during the time since cortisone. In the patients operated on before cortisone the degree of resection was limited by fear of postoperative cortical insufficiency, and the results were inadequate. Of the 7 who never received cortisone the first 2 died with active Cushing's disease unaffected by the removal of 30 per cent of the adrenal tissue. In 2 others the removal of 30 per cent brought improvement but neither complete nor permanent relief; 1 has had a further operation elsewhere, and 1 is living with smoldering disease and thus far refuses further operation. The remaining 3 are living without evidence of active disease although 2 of these have not recently returned for evaluation.

TABLE 5. *Operative Results in 27 Patients with Hyperplasia.*

OPERATION	NO. OF CASES	RESULT			
		PATIENTS WHO DIED WITH ACTIVE DISEASE	PATIENTS WHO DIED AFTER RELIEF OF DISEASE	PATIENTS LIVING WITH ACTIVE DISEASE	PATIENTS LIVING & RELIEVED OF DISEASE
None	2	2	0	0	0
Partial resection only	2	2	0	0	0
Subtotal resection	23	0	2	2	19
Totals	27	4	2	2	19

Of the 18 patients whose surgical treatment has been completed since the advent of cortisone, 2 have died, 1 six days after operation of a pulmonary embolus, and the other of renal sepsis two months after operation. One was lost to follow-up study five months after operation. The remaining 15 are living and well one to six years after operation. The average estimated resection in these 18 cases was 89 per cent. Five of the 15 "cured" patients require cortisone regularly in low doses to maintain a state of health or require added cortisone during infections or other periods of stress to avoid cortical insufficiency. All these patients have had 80 per cent or more of their estimated total adrenocortical tissue removed. The groups are summarized in Table 5.

In summary, in this series, 29 of 34 patients who underwent either subtotal adrenalectomy for hyperplasia or total excision of a benign adenoma are now living without evidence of active Cushing's disease.

COMMENT

The more we have seen of Cushing's disease, the more we have come to realize that it is a disease of the adrenal cortex in much the same manner that

Graves's disease is a disease of the thyroid gland. There are many similarities between Graves's disease and Cushing's disease. Both appear in the same kind of people, have a comparable theoretical relation to the anterior pituitary body and perhaps have the same sort of etiology.

Cushing's disease is predominantly a disease of the female. Four times as common in the female as in the male in our series and three times as common in the cases reported in the literature,[55] it appears most frequently during the active phase of ovarian life. Graves's disease has the same sex and age distribution.

The development of both diseases is associated with the same kind of psychologic stress situations and anxieties. We are also impressed by the frequency of occurrence of acute endocrine changes, such as pregnancy, at or just before the time of the initial clinical manifestations of the diseases.

In spite of the frequency of associated psychologic and endocrine difficulties it must be admitted that the etiology of Cushing's syndrome is still obscure. The physical changes induced by the disease are psychologically disturbing, and the emotional changes encountered in patients with the disease may be the result of it rather than its cause. The process may have been latent and only made manifest by pregnancy or its termination in women in whom the disease seemed to appear on the heels of a pregnancy.

The anterior pituitary body appears to bear much the same relation to both diseases. In recent years experimental and clinical evidence has accumulated indicating that overactivity of the thyrotropic stimulus of the anterior pituitary body is essential to the development of Graves's disease.[25] Irradiation of the pituitary gland is sporadically successful in halting active hyperthyroidism.[56] In similar fashion there is now much evidence that the adrenocorticotrophic action of the anterior pituitary gland bears a similar relation to overactivity of the adrenal cortex. Here, too, irradiation of the pituitary gland sporadically arrests the manifestations of Cushing's disease. Injection of the adrenocorticotrophic hormone (ACTH) can reproduce in entirety the clinical picture of spontaneous Cushing's disease.

At present the practical therapeutic attack in Cushing's disease is upon the end organ of endocrine action as it is in hyperthyroidism. The object of attack is the thyroid gland in hyperthyroidism and the adrenal cortex in Cushing's disease. In the latter, the therapy is surgical. There is as yet no medical treatment comparable to the antithyroid drug or radioactive-iodine therapy of hyperthyroidism.

Summary and Conclusions

Since 1935, 46 patients with Cushing's disease have been cared for at the Massachusetts General Hospital. Suppression of the action of the anterior pituitary gland either by irradiation or by hormones has proved only sporadically successful. Surgery has emerged as the consistent practical therapy.

The disease is one of overactivity of the adrenal cortex much as Graves's disease manifests itself by overactivity of the thyroid gland. The anterior pituitary gland appears to bear much the same relation to both diseases.

When the disease is caused by a tumor of the adrenal gland the problem is complete removal of the tumor, leaving the contralateral uninvolved gland. A neoplasm was found to be the cause in 17 of our cases. In 5 patients the tumor was malignant, and all succumbed with metastatic disease. The other 12 had benign neoplasms. One died before operation; 11 survive, cured by resection.

Bilateral hyperplasia, accounting for 27, was treated by subtotal resection. In 2 cases the hyperplasia was associated with multiple nodules, a phase of the adrenal change believed comparable to nodular goiter with hyperthyroidism. To achieve a consistent therapeutic result in the hyperplasias it has been found necessary to remove at least 90 per cent of the adrenocortical tissue. Of the 27 patients 2 died before operation; of 4 with a limited resection 2 have died of active disease, and 2 are living with residual disease; 2 others have died after surgical relief of the disease; 19 are living and cured.

Cortisone has facilitated an adequate surgical attack, particularly in cases due to hyperplasia of the adrenal cortices. In addition to the use of cortisone to offset acute cortical insufficiency, management of the postoperative phase requires an understanding of an acid nutritional need as healing occurs.

We are indebted to many for much advice, in particular to Dr. Joseph C. Aub, who in 1931 first interested us in this disease; to Dr. Fuller Albright, with whom we have shared most of the experience; to Dr. Benjamin Castleman for thoughtful criticism; to Dr. Edward D. Churchill and the Surgical Staff of this hospital, who have entrusted to us the care of the patients; and to generous anonymous donors for the colored illustrations.

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METHYLPHENYLSUCCINIMIDE (MILONTIN) IN EPILEPSY*

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FAVORABLE results with methylphenylsuccinimide in the treatment of epilepsy were reported first by Zimmerman[1] and later by Zimmerman and Burgemeister,[2] Millichap,[3] Smith and Forster,[4] Carter,[5] Lemere,[6] Lereboullet[7] and Chao and Fields,[8] although the last named combined the drug with Tridione. The treated cases numbered 15 to 200. In contrast, Doyle, Livingston and Pearson[9] encountered flat failure in 21 cases. Our observation of 296 persons treated with methylphenylsuccinimide during a period of three years suggests that the drug is of value.

MATERIAL AND METHOD

Patients were seen by one of us, either as clinic or as office patients in the Seizure Unit of the Children's Medical Center in Boston. The series, like that of Doyle, Livingston and Pearson,[9] is heavily weighted on the side of youth, 4 out of 5 being less than nineteen years old. As a consequence, petit mal is more commonly represented (63 per cent of 249 patients) than would be true in a predominantly adult series. In fact 83 per cent of our patients displayed either a petit-mal-triad seizure pattern or a spike-wave complex on the electroencephalogram.

The daily dosage for an infant was usually 0.5 gm. (half the contents of a 0.5-gm. capsule with the morning and evening meals). Children to the age of four years received 1.5 to 2.0 gm. a day, those from four to nine years, 2.0 gm., and those above nine years 2.5 gm. The dosage was increased at the rate of 0.5 gm. a day every two weeks until either seizure control was obtained or toxic symptoms appeared. The maximum daily amount was 5.0 gm.

Patients or parents were told that results, whether good or bad, could not be predicted for any particular case, and, therefore, that careful observation and accurate recording would form the basis for evaluation of the results. Mimeographed progress sheets dealing with day-to-day observations were submitted by the patient each month. These provided for a daily record of seizures, side effects of the drug, intercurrent illnesses, incidents that were productive of emotional stress and marked deviations from the usual diet. Insufficient data or incomplete trial necessitated the rejection of 45, or 15 per cent, of the 296 patients to whom methylphenylsuccinimide was initially given. Cases in which toxic symptoms developed are included in Table 1, but some of these patients did not take the drug long enough to permit evaluation of seizure control.

Suspected evidences of toxicity were reported by telephone, and the presence of rash, vomiting, urinary symptoms or excessive sedation called for reduction or withdrawal of the drug. A total and differential count of leukocytes was made monthly. The urine was examined in all cases in which urinary symptoms appeared and also in a group of 61 asymptomatic patients who had taken the compound for periods up to three years at an average dose of 2.5 gm. a day. An electroencephalogram was taken before treatment was started at intervals of three to twelve months thereafter. Therapeutic results were evaluated monthly.

TABLE 1. *Frequency of Side Effects.*

SIDE EFFECT	NO. OF CASES	PERCENTAGE
Sedation	29	10
Ataxia	16	5.4
Irritability	16	5.4
Rash	13	4.5
Nausea, vomiting or anorexia	10	3.4
Headache	7	2.4
Urinary frequency or burning	5	1.7

In the beginning methylphenylsuccinimide was used only for patients whose seizures resisted control with the conventional and proved drugs. Observation of more than 100 patients demonstrated a lack of serious toxicity and also a particular effectiveness against petit mal. Because of this and because Tridione or Paradione occasionally causes depression of the bone marrow, we began to use methylphenylsuccinimide as the initial drug for petit mal. It was given alone whenever feasible but was added to previous medication when that had not caused toxic symptoms and had exerted only partial seizure control. Combined therapy was especially necessary if convulsive seizures, as well as petit mal, were present. When previous medication was reduced or eliminated, a suitable observation period was allowed to intervene before methylphenylsuccinimide therapy was begun. The dosage of only a single drug was changed during any period of observation. Results, when equivocal, were often checked by withholding of Milontin.

RESULTS

Many variables influence the frequency and severity of epileptic symptoms. In childhood, especially, the frequency or severity of seizures may change spon-

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taneously. Emotional stress, associated with scholastic or social adjustments, may increase or the amelioration of stress may decrease seizures. In view of these considerations, under the best of conditions, estimation of a patient's response to a given drug will be only a rough approximation of the truth.

The total over-all results were estimated for the whole group of 249 persons (Figure 1). Findings regarding the estimated degree of improvement were

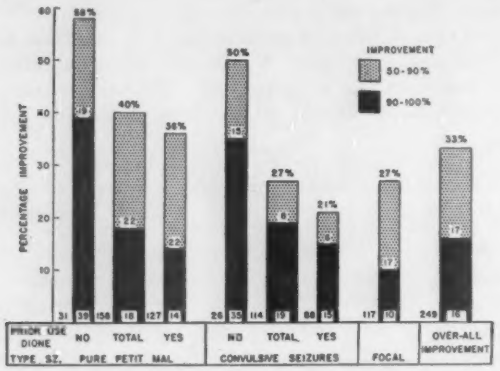

FIGURE 1. *Degree of Improvement with Methylphenylsuccinimide.*

The number 249 on the far right refers to the total number of patients. Corresponding numbers near the base of the other columns refer to seizure patterns. Certain patients had more than one type of seizure—hence, the total of 389 seizure patterns and only 249 patients. Focal seizures include psychomotor attacks.

tabulated. A third were deemed to be having 50 to 100 per cent fewer seizures as a result of taking methylphenylsuccinimide (right-hand column, Fig. 1). Many of these persons had more than one type of seizure, and the results with three different seizure patterns are listed. Of the 114 patients subject to convulsive seizures (fourth column from the right), 1 in 5 had 90 to 100 per cent, and 1 in 12 50 to 90 per cent fewer convulsions. Thus, a total of slightly more than a quarter were more than 50 per cent improved. The improvement in nearly three fourths (73 per cent) was less than 50 per cent or nil. Results were least favorable (next to last column) for the 117 with focal elements to their seizures (only 10 per cent with control of at least nine tenths of seizures).

Patients subject to pure petit mal fared best. Of the 158 persons (second column), 40 per cent were rid of more than half their attacks. Counted also (but not entered in the table) were the persons completely free of seizures while taking the drug (alone or with other medicines). Fourteen per cent of the total of 249 were seizure free, and 2 per cent had lost 50 to 90 per cent of the level before therapy. However, after our tabulation had been completed some "controlled" cases escaped full control. Hence, results in these two groups are consolidated in Figure 1. In the series of patients with petit-mal seizures described by Zimmerman and Burgemeister[2] the proportion of those under complete control fell from 30 to 21 per cent in a period of fifteen months.

Our data show more benefit for convulsive seizures than those given by other authors. Carter[5] recorded numbers of major and minor attacks in 81 institutionalized patients. Under treatment minor attacks decreased by 35 per cent, but the major ones increased by 21 per cent. Our series contained an unusual number having both petit and grand mal. If a flurry of petit mal initiated a grand mal, control of the former occasionally prevented the latter. The majority of these patients were receiving standard anticonvulsant drugs, but since the dosage was held constant, it is reasonable to attribute any improvement to methylphenylsuccinimide.

Influence of Previous Therapy

The majority of patients with petit mal had been treated without continuing success with Tridione or Paradione, or both. Figure 1 displays the degree of benefit for persons who previously had or had not been given one or both of these drugs. Those rid of nine tenths of petit mal (third column) formed 14 per cent of the group previously treated with a dione but 39 per cent of those not so treated (first column). Thus, it is evident that methylphenylsuccinimide was more often effective in patients whose petit mal had not been treated than in those resistant to dione therapy. On the other hand, we found that some patients resistant to the newer compound could be controlled by Tridione or Paradione or a combination of a dione with methylphenylsuccinimide.

Convulsions also were more readily controlled if there had not been previous failure with diones. Of 88 persons with prior use (sixth column), only 15 per cent experienced nearly complete control, but of 26 without prior use (fourth column) this degree of improvement occurred in 35 per cent.

Influence of Electroencephalogram

Cases were divided into two groups. The electroencephalograms of the first contained the characteristic rhythmic three-per-second spike-wave complexes. Those of the second group had two-per-second or irregular complexes or other types of irregularity. Of the patients with petit mal, 46 per cent in the first and 33 per cent in the second group had more than a 50 per cent improvement. Of patients who had convulsions but whose electrocardiograms were in the first group 44 per cent had that degree of improvement against 22 per cent of those in the second group.

Influence of Brain Damage

Evidence of some degree of brain injury was present in about a seventh of persons with pure petit mal, a third of those with convulsions and half those with minor seizures that were not pure petit mal. The benefit from the use of methylphenylsuccinimide was not significantly reduced in patients with injury and petit

mal but seemed about a third less effective in those with injury and other forms of epilepsy.

Neither age, sex nor (within limits) dosage seemed to influence results.

Long-Term Results

As suggested by Zimmerman and Burgemeister[2] initial benefit experienced by patients may not be sustained. A period of eighteen months has elapsed since the foregoing results were tabulated. We are making a follow-up study of the patients treated to determine this point.

Side Effects

No serious toxic signs were observed in the total number of 296 patients, although a few experienced one or more minor side effects. The frequency with which these were mentioned is shown in Table 1. Doses that exceeded the limit of tolerance usually produced sedation, ataxia or irritability. Rash occurred only in patients under nineteen years of age. The eruption was usually of a maculopapular type that appeared after eight to twelve days, first on the face and distal extremities. In 1 case it was urticarial. The majority of the patients were able to continue medication after a temporary reduction in dosage. Only in 1 case was the rash resistant to desensitization by administration of small doses at longer intervals. Erythema multiforme was present in 1 of Millichap's[3] patients.

Urinary frequency and burning appeared in 2 boys and 3 girls. All but 1 of these patients were receiving higher than average dosage, their range being 2.5 to 5 gm. daily. Urinalyses revealed occasional red blood cells in the sediment in 3 and no abnormality in 2 of these children. In all, symptoms disappeared promptly after reduction in dosage, and subsequent urine examinations were negative.

A spot check of the urine of 61 patients who had taken the drug in doses as high as 3.5 gm. a day for periods up to three and a half years disclosed the following results: red blood cells per high-power field, "rare," "1 or 2" or "occasional," 7 cases; sugar, "+" or "trace," 4 cases; and albumin, "slight trace" or "+", 3 cases, and "heavy cloud" in 1 case. No casts were reported in any case.

Despite the rare finding of microscopical hematuria in our patients and in those of other investigators[5,8] no case of persistent hematuria or chronic renal toxicity was observed.

Summary and Conclusions

Methylphenylsuccinimide (Milontin) was given to a selected group of 296 patients in a period of three years. No serious side effects were encountered. Sedation, ataxia, irritability and rash, in that order, occurred in 10 to 5 per cent.

Among 249 patients adequately followed seizure control was most effective for persons with pure petit mal and for those with three-per-second spike-wave discharges in the electroencephalogram. Petit-mal attacks were reduced by more than half in 40 per cent of patients, in 36 per cent if a dione had been employed in the previous control period and in 58 per cent if it had not been used.

Convulsions were also fewer (27 per cent of grand-mal patients had less than half as many). However, in these cases, anticonvulsant drugs were also employed.

Because blood dyscrasia, liver toxicity, psychosis or other serious side effects have not been encountered this drug may logically be used as the initial treatment of pure petit mal.

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REVIEW OF FIFTEEN YEARS' EXPERIENCE WITH GASTRECTOMY IN A COMMUNITY HOSPITAL

I. Ulcer

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THIS report is based on a study of the total experience with gastrectomy at the Salem Hospital during a fifteen-year period, 1939-1953. Three hundred and eight gastrectomies were performed by 26 surgeons. Indications for gastrectomy are listed in Table 1.

TABLE 1. *Indications for Gastrectomy.*

INDICATION		NO. OF CASES
Complicated duodenal ulcer		153
Gastric ulcer		101
Gastric carcinoma		46
Miscellaneous		8
Massive bleeding, cause not revealed by gastrectomy	3	
Leiomyoma	2	
Chronic gastritis	1	
Prolapsing gastric mucosa	1	
Ectopic Brunner's glands	1	
Total		308

The contrast between increasing frequency of gastrectomy for ulcer disease and the fairly constant number for gastric carcinoma is striking (Fig. 1). A study of a fifteen-year period was made to minimize the error potential of an inadequate number of cases. It is appreciated that certain statistics such as the mortality rate must necessarily suffer by comparison with rates cited in current articles based on a more recent period of observation.

The majority of articles on gastrectomy come from larger hospitals and university centers, but it seems probable that the major portion of gastrectomies are performed in smaller hospitals where the volume of operations and the experience of surgeons are similar to those in the Salem Hospital. Stimulating reports from such smaller hospitals have appeared during the past two years.[1-3] The conclusions in the present article are based on a study of experience at Salem Hospital, recent surgical literature and personal communications with various authorities on gastric surgery.

MATERIAL

The Salem Hospital is a community hospital of 240 beds, located 15 miles from Boston and adjacent to similar hospitals within a 5-mile radius, in Lynn and Beverly. The current yearly total of admissions is approximately 9000.

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Gastrectomy was performed on 38 per cent of hospitalized patients in whom a diagnosis of gastric carcinoma was made and on 22 per cent of those hospitalized because of gastric or duodenal ulcer. The same percentage of patients had a gastrectomy regardless of whether the ulcer was located in the stomach or in the duodenum. Currently, gastrectomy is much more frequently proposed for patients with gastric ulcers.

Nine of 308 gastrectomies were done by 3 Boston consultants. Two hundred and sixty gastrectomies were performed by 11 members of the surgical staff of the Salem Hospital, none of whom did more than 7 gastrectomies at the Hospital in any year of this study. Thirty-nine operations were performed during the past seven years by 12 residents in surgery, each of whom comes to Salem Hospital for a six-month

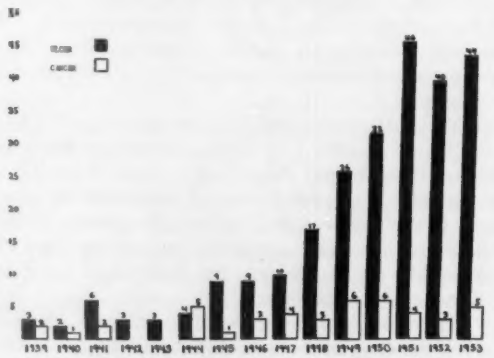

FIGURE 1. *Increasing Frequency of Gastrectomy at the Salem Hospital, 1939-1953.*

period as part of a training program with the Massachusetts General Hospital. Nine surgeons on the staff of the Salem Hospital are fellows of the American College of Surgeons, and 4 are also members of the American Board of Surgery. Complications and mortality are carefully reviewed once a month by the entire surgical staff.

Excellent roentgenologic, laboratory and anesthesia services are available. These services are provided by full-time physicians. The chief of each service is a member of his respective specialty board.

Roentgenology

Two types of problem are especially troublesome both to surgeon and to radiologist: massive upper gastrointestinal bleeding and gastric ulceration.

Massive bleeding. Immediate x-ray examination of the esophagus and stomach is attempted in all patients admitted with such profuse bleeding, unless their condition prohibits. The "no-hands" technic of barium survey as suggested by Hampton[4] is employed. This method can localize the source of massive blood loss not due to esophageal varices or blood dyscrasias in about 50 per cent of the cases. When varices are present they can almost always be detected. Frequently, a small gastric ulcer may escape detection by x-ray study, even in a patient who is not bleeding profusely, despite the best efforts of the radiologist. The urgency of identifying the probable source of profuse blood loss from lesions in the stomach or duodenum has seemed so imperative that in my own cases I have asked the radiologist to conduct a more detailed study of the gastric contour, mobilizing the pool of barium in the stomach by manual displacement and change of the patient's position. The danger of provoking additional blood loss by such maneuvers has not seemed to be as great a hazard as failure to demonstrate ulceration in the gastroduodenal region.

Gastric ulceration. The accuracy in detecting a benign or carcinomatous ulcer of the stomach is about 85 per cent if only a single examination is made. However, a correct diagnosis may be made in 95 per cent if repeated x-ray survey is made after satisfactory medical treatment of the hospitalized patient. Diagnostic features of peristalsis and outline of profile are more difficult to visualize in the radiologic blind spot, the proximal half of the stomach, which functions as a reservoir, in contrast to the right half, where the bulk of mixing and propulsion takes place. The present series included occasional cases both of small gastric ulcers associated with profuse bleeding not detected in preoperative x-ray study and of small gastric ulcerations due to carcinoma that had appeared to be benign ulcers on initial x-ray examination.

The difficulty of the radiologist's task is more easily appreciated if the surgeon observes the fluoroscopic study of some of his patients.

Cytology

Few gastric aspirations have been sent to the laboratory for cell study. The employment of the abrasive balloon[5] or the gastric brush[6] is said to provide a greater volume of desquamated epithelial cells than is obtained by simple aspiration. Cooper[3] states that this diagnostic aid "is at least as accurate as the x-ray." Graham,[7] who is convinced that cytologic study of simple gastric aspirations can be rewarding if adequate attention is devoted to the technic of collection of specimens, reports an accuracy of 80 per cent in patients with gastric ulceration at the Massachusetts General Hospital, provided the aspirate is properly obtained and immediately taken to the laboratory for preparation.

Gastric acidity. Acidity had not been determined in every case of gastric ulcer in this series. Diminished or absent gastric acidity is found in 75 per cent of gastric carcinomas.

Massive bleeding. In patients with massive bleeding from ruptured esophageal varices secondary to cirrhosis of the liver the hospital laboratory has been of great assistance in the determination of extent of blood loss and in the maintenance of a blood bank. Liver-function tests such as thymol turbidity, cephalin flocculation and prothrombin time are often of considerable aid in diagnosis. These values will not be affected by hemorrhagic shock, in contrast to the levels of bromsulfalein excretion. A platelet smear, bleeding and clotting times and prothrombin time help to disclose blood dyscrasias. Such tests and immediate x-ray survey of the esophagus were requested on admission in a number of patients in whom the diagnosis was uncertain. Few blood-volume determinations by the dye-dilution technic have been done, but it is apparent that daily or fractional-dose blood-volume determinations are helpful in management of patients hemorrhaging from the gastrointestinal tract. This test is not too complicated for most hospital laboratories. The fallacy of reliance on the red-cell count, hemoglobin or hematocrit in the evaluation of continuing blood loss is well known.

Fluid and electrolyte service. Guides for the establishment of such a service have been presented by Nickerson,[8] director of laboratories at the Salem Hospital. A flame photometer is available. It is my impression that this service has repeatedly speeded convalescence and probably saved lives.

Eighteen autopsies were performed on 44 patients who died after operation (including 4 of my 5 patients). Such examinations have been a source of accurate information in a number of cases when the clinical picture was not altogether clear.

Anesthesia

Three full-time physicians administer anesthesia exclusively at the Salem Hospital. During the first portion of this fifteen-year period spinal anesthesia was commonly employed and frequently had to be supplemented. In the last seven years endotracheal nitrous oxide, oxygen and ether anesthesia has been used almost exclusively. Pentothal and the muscle relaxants assume an increasing role as supplements.

Gastrectomy for Duodenal Ulcer

In 1939 only 1 gastrectomy was done because of duodenal ulcer. During the past three years, 40 or more have been done each year because of complicated duodenal ulcer. Articles continue to appear each year under the title, "Gastrectomy For Peptic Ulcer," in which the cases include both gastric and duodenal ulcers. However, fear of the small, ulcerating carcinoma prompts separate consideration. It is recognized that hypersecretion and hypermotility are etiologic factors in both gastric and duodenal ulcers and that similar indications for surgery such as

hemorrhage and pyloric obstruction are often present in both groups (Table 2).

The technical problems and complications of gastrectomy have been dissimilar in my experience. In duodenal ulcers, postoperative morbidity and mortality have been due principally to complications of dissection and closure of the difficult duodenal stump. Pancreatitis and duodenal fistula naturally occur less often after gastrectomy for a gastric ulcer. Wider choice in the technic of restoration of gastrointestinal continuity may be available in the gastric ulcer since a normal uninflamed duodenum may invite a gastroduodenostomy.

Although no immediate gastrectomies have been done for perforated ulcers, it is apparent that gastric resection is a better operation, in an occasional case, than simple suture of the perforation. Twenty-two per cent of patients hospitalized because of complicated duodenal ulcer required gastrectomy. This figure lies between the 25 per cent cited by Moore et al.[9] and the 16 per cent cited by Glenn and Harrison.[10] During the past eight years gastrectomy has been proposed more readily to the patient both by his own doctor and by surgeons at this hospital and has been accepted more promptly by the patient than during the first seven years of this study.

TABLE 2. *Indications for Gastrectomy for Duodenal Ulcer.*

INDICATION	NO. OF CASES
Hemorrhage	49
Intractability	61
Pyloric obstruction	32
Multiple conditions	9
X-ray diagnosis of pyloric carcinoma	1
Clinical diagnosis of pyloric carcinoma	1
Total	153

The purpose of this study was to determine whether gastrectomy was being done too frequently or often enough on patients with complicated duodenal ulcer, how much stomach should be removed, whether the ulcer should be included in the resection done for bleeding or intractable ulcer and how the *inoperable* duodenal ulcer should be managed. Finally, it was hoped to assess the operative mortality at the Hospital. Discussion of indications for surgery was warranted only in the 110 cases in which bleeding or intractability was of first importance.

Hemorrhage

Gastrectomy was performed in 49 patients (32 per cent) because of profuse bleeding. In 41 cases elective operation followed recovery from initial bleeding. Emergency gastrectomy was done in 8 patients. Two of the patients in the 41 elective cases died (4.7 per cent). Two of the 8 (25 per cent) operated on as emergencies died. In each of these 8 cases the surgeon expressed the opinion that the patient would succumb unless operated upon. The degree and rate of blood loss divide the patients into three classes: those with massive hemorrhage before admission with some degree of shock present at admission; those with profuse hemorrhage in the hospital on a satisfactory medical regimen; and those with continued bleeding evidenced by rapid pulse, lowered blood pressure, guiac-positive stools and failure to maintain adequate hemoglobin levels despite blood replacement. Stewart et al.[11] claimed gratifying results with immediate blood replacement and simultaneous gastrectomy. In Welch's[12] experience it is preferable to carry out gastrectomy at a time of election when the patient's condition and rate of blood loss permit; this has also been my experience. It has been established that massive bleeding from a duodenal ulcer ceases spontaneously in 75 per cent. However, an occasional patient, young or old, will die from continued bleeding unless an emergency gastrectomy is performed. It is widely acknowledged that prognosis becomes poorer with each day of continuing blood loss before gastrectomy despite efforts at quantitative replacement of blood. Hoerr, Dunphy and Gray[13] emphasize not only the amount of blood loss but also the rate. Ingelfinger and Sanchez[14] have recently discussed indications for immediate operation from the standpoint of the internist.

No attempt has been made at Salem Hospital to define exact indications for emergency gastrectomy since there are so many variable factors in the patient, the ulcer, the blood loss and the surgeon. No emergency gastrectomies were performed for bleeding ulcers before 1946. Clinical observation of progressive change in the patient's color, pulse, respiratory rate, urinary output, blood pressure, skin temperature and degree of anxiety has proved helpful. The value of serial blood-volume determinations has been mentioned. A recent case illustrates the role of routine nasogastric suction in profuse blood loss from the gastrointestinal tract, even in the absence of vomiting.

M.F., a 66-year-old woman, had profuse melena. She had no symptoms to implicate the stomach. X-ray studies failed to reveal esophageal varices or gastroduodenal ulceration. She had been hospitalized for 1 week and had received 12 transfusions when profuse hematemesis provided the first clue to ulceration proximal to the ligament of Treitz. Emergency gastrectomy was performed. At operation no area of disease could be detected in the stomach or duodenum. A rapid 75 per cent gastrectomy was carried out. An ulcer, 1.5 cm. in diameter with a central, eroded artery, was found high on the anterior wall of the stomach close to the proximal margin of resection.

Routine nasogastric suction from the time of admission would probably have disclosed fresh bleeding earlier than the occurrence of hematemesis.

Gastrectomy is proposed for patients with massive bleeding who have previously bled or have a long ulcer history, previous hospitalization or pyloric obstruction. Formerly, patients with profuse bleeding were admitted to the medical service and not examined routinely at admission by a surgeon. During the past six years such patients have become the immediate and continuing responsibility of both services regardless of the ward on which they reside.

Intractability

Intractable ulcers were present in 61 patients. The term "progressive virulent ulcer" has been proposed by Moore and his associates[9] as a substitute for "intractable." Such terminology seems reasonable when one considers the repeated episodes of disability, multiple hospital admissions (22 in 1 case), previous bleeding, clinical and x-ray evidence of varying degree of pyloric obstruction and periodic bouts of pain in this series of patients. Decision for gastrectomy is more difficult for both internist and surgeon in such cases than in those in which copious bleeding or frank pyloric obstruction has occurred.

Thirty-eight patients had an average of 3.6 admissions in the effort to control duodenal ulcer. In the other 23 cases gastrectomy was performed at the first admission, but the average duration of symptoms was eight years, being less in only 4 cases, and in all of these an indurated, penetrating duodenal ulcer had been demonstrated by x-ray study.

In the light of current surgical accomplishment it is apparent that too many patients in this series have been permitted to endure too much discomfort and disability for too long a time before gastrectomy. A more accurate appraisal of this group might have resulted from joint review by both surgeon and internist. Elective gastrectomy may be resorted to more readily in an institution where the surgical mortality is 2 per cent or lower than in this hospital, where the rate was 7 per cent for this fifteen-year period.

Gastrectomy for duodenal ulcer is designed to accomplish the following goals: removal of the entire antrum to eliminate secretion of the histaminelike substance that spurs manufacture of hydrochloric acid by the parietal cells; removal of approximately 75 per cent of the stomach to eliminate the major portion of acid-forming parietal cells; removal of almost all the lesser curvature; and excision of the duodenal ulcer when feasible. There is general agreement that approximately 85 per cent of patients obtain good results from such an operation.

It is difficult to make an accurate estimate at operation of the amount of stomach that has been removed. Harkins[15] has actually measured both curvatures of the stomach before and after resection. Rough guides to an adequate length of lesser and greater curvature (10 cm. and 20 cm.), suggested by Welch,[16] have been valuable in a review of the dimensions of the operative specimens in this series. It is obvious that a larger portion of the stomach was removed during recent years than in the earlier period. A good number of resected stomachs fall somewhat short of these measurements. Postoperative x-ray films of the gastric remnant were available in only a few patients.

It has long been recognized that stomach ulceration may follow an inadequate removal of the stomach. No case of postoperative stomal ulcer was encountered. Currently, attention is being given to the number of undesirable, postgastrectomy complaints such as indigestion, poor appetite, weight loss and inability to maintain satisfactory hemoglobin levels. Harvey, St. John and Volk[17] conclude that the higher percentage of digestive difficulties may logically be ascribed to the greater amount of stomach removed in more recent operations. Less stomach should be removed in women, in underweight patients[18] and in patients with dilated stomach from preoperative obstruction.

Hemigastrectomy and vagotomy have been proposed by Farmer and Smithwick.[19] Since only 50 per cent of the stomach is removed it is argued that better gastric digestion is obtained. The addition of vagotomy is said to reduce gastric acidity even more than a 75 per cent gastrectomy. Crile,[20] previously enthusiastic for vagotomy and gastroenterostomy, now performs a 50 per cent gastrectomy and vagotomy in about 75 per cent of patients, reserving vagotomy and gastroenterostomy for the additional 25 per cent whose ulcers are penetrating and in whom closure of the duodenal stump promises to be difficult. Wangensteen[21] proposes still another technic of gastric resection (tubular gastrectomy). He comments, "The ideal operation for peptic ulcer has not yet been devised." Allen,[22] McKittrick,[23] Glenn,[10] Harvey et al.[17] and Welch[16] suggest that perhaps 50 per cent of the small number of patients who are dissatisfied after gastrectomy would not be entirely free of symptoms, regardless of the operation performed, because of their labile nervous system. Only time and the accumulation of considerable experience will prove the value of the more recent surgical technics. Currently, enthusiasm for vagotomy and posterior gastroenterostomy is on the wane although the procedure continues to enjoy deserved popularity in the management of inoperable duodenal ulcers or stomal ulceration after gastrectomy. I am not aware of any significant number of postoperative patients in this series who are suffering from impaired digestion. Removal of approximately 75 per cent of the stomach should continue to be a goal.

The resection of the offending duodenal ulcer provides a second major challenge to surgical skills.

Ulcer in the First Portion of the Duodenum

The ulcer was excised in only a third of 153 cases. Several surgeons have repeatedly urged the desirability of inclusion of the ulcer in the resection.[24] Thompson and Stewart[25] believe that failure to remove the ulcer plays a part in the development of subsequent gastrojejunal ulcer. A proximal transection of the duodenum was usually done in the present series unless the ulcer was located in the first portion of the duodenum and its bed permitted excision without apparent jeopardy to surrounding structures. The duodenum was transected through, rather than beyond, the ulcer if a more secure closure was thereby obtained. Excision of the ulcer did not influence the postoperative results in this series.

The Bleeding Ulcer

The ulcer was excised in 12 patients (25 per cent) and left in situ in 37 (75 per cent). Only 3 patients in whom the bleeding ulcer had not been excised are known to have bled after gastrectomy. This subsequent bleeding was profuse in all 3 patients and fatal in 1.

G.B., a 79-year-old man, had an emergency gastrectomy at 8:00 p.m. a few hours after transfer from a smaller hospital. He had received 10 transfusions during the previous 5-day period. The huge, deeply penetrating ulcer, low in the 2d part of the duodenum, was found (Fig. 2). The duodenum was transected proximally without clamps. No bleeding was seen. Removal of the ulcer seemed unwise because of the patient's condition and the size and location of the ulcer over the lower end of the common duct. This elderly patient did very well for 7 days, had begun to eat regularly and was up and walking about when he again bled massively. Vital signs were quickly stabilized by the administration of 1000 cc. of blood by pressure transfusion. However, he again bled massively and fatally on the 9th postoperative day. The eroded artery in the ulcer is shown in Figure 2.

FIGURE 2. *Nonresectable Duodenal Ulcer from Which a Fatal Hemorrhage Occurred Nine Days after Emergency Gastrectomy.*
The ulcer is located low in the duodenum, overlying the lower end of the common duct.

Hinton[26] emphasizes the fact that bleeding ulcers must be removed to avoid later deaths from additional hemorrhage. Direct mattress suture of this bleeding vessel would have been undertaken if bleeding had been continuing when the ulcer was exposed. The gastroduodenal artery was not ligated because of the difficulty in identifying this artery in the indurated tissue beyond the pylorus and the probability that collateral circulation from the inferior pancreaticoduodenal artery was present to promote the continuance of bleeding. Cole[27] states, "Ligation of an artery such as the gastro-duodenal artery is almost entirely inadequate to control hemorrhage in most cases." Stewart,[11] outstanding exponent of gastrectomy for bleeding duodenal ulcers, has left the ulcer in situ in 23 out of 56 gastrectomies done because of acute bleeding.

The other horn of the dilemma is illustrated by the following case:

V.L., a 54-year-old woman, had an emergency gastrectomy on the 2d hospital day after 3 episodes of gross bleeding. The ulcer in the 2d portion of the duodenum was densely adherent to the pancreas. The bleeding ulcer was removed by gentle, sharp dissection. The duodenal stump was satisfactorily closed, with minimal trauma to the adjacent pancreas. The patient walked on the 2d postoperative day. Thereafter, signs of acute pancreatitis developed, confirmed by peritoneal tap, which was positive for trypsin. At reoperation on the 12th day sump drainage to the region of the head of the pancreas was done. She died on the 16th day. Post-mortem examination demonstrated acute pancreatic necrosis with an intact duodenal stump.

Pancreatitis might have occurred even if such sharp dissection of the duodenum from the head of the pancreas had not been required. Warren[28] describes several fatal cases of pancreatitis after gastrectomy for gastric ulcer in which there had been no significant amount of dissection around the pancreas. Nevertheless, such an experience suggests that more patients might die of postoperative complications after difficult dissection than of bleeding from the unremoved ulcer.

The Inoperable Duodenal Ulcer

The importance of early recognition of the hazardous duodenum and adoption of appropriate procedure in its management is emphasized by the fact that 10 of the 11 postoperative deaths in this series resulted from either postoperative pancreatitis or peritonitis. Welch[16] observes that the percentage of nonresectable bleeding ulcers rises appreciably when the surgeon has had less experience. Post-mortem examination revealed a leaking duodenum in 4 of 8 deaths from peritonitis. Nowhere in gastric surgery can the experience and judgment of the operator be exhibited to better advantage than in his choice of procedure when confronted with a difficult duodenum. It is difficult to appraise the required duodenal dissection accurately, at a reversible stage in the operation. Without question a greater number of difficult resections and safe closures can be done by the experienced surgeon in comparison with the operator who may be performing only one gastrectomy a month. Crile,[20] reporting a mortality of 0.5 per cent in elective surgery for duodenal ulcer, employs gastroenterostomy and vagotomy in 20 to 30 per cent of cases in which safe closure of the duodenal stump promises to be difficult. Many surgeons report a lower rate of nonresectable ulcers.

Numerous operative procedures are suggested for management of the difficult duodenum: vagotomy and posterior gastroenterostomy, catheter drainage of the transected duodenum, the McKittrick two-stage gastrectomy, plastic closure of the duodenum distal to the ulcer (Graham) and the Bancroft operation.

Catheter duodenostomy[29] was performed in 4 patients. Allen,[30] in 16 cases, found catheter decompres-

sion of the insecure duodenal stump to be "a very good way out of a difficult situation." Accurate fluid and electrolyte replacement is, of course, imperative since profuse duodenal drainage begins on about the third day. There has been 1 death in this series from postoperative acute pancreatitis despite minimal surgery on an inflamed duodenum and the institution of catheter drainage. The alarming mortality from fistula or pancreatitis in this series emphasizes the need for employing either catheter duodenostomy or vagotomy and gastroenterostomy more frequently. Some surgeons routinely place a drain at the site of the closed duodenum. Surely, as Welch points out, deliberate decompression of a friable, inflamed duodenum provides more effective control of a duodenal fistula than insertion of a drain in the region of an *insecurely closed* duodenal stump.

Recently, from the Boston City Hospital,[31] 13 cases of duodenal fistula were reported after gastrectomy for duodenal ulcer. In only 1 patient were early reoperation and drainage carried out. This patient died. In the Salem Hospital surgeons have temporized in the past, when a duodenal fistula was first suspected in the immediate postoperative period. These patients also died. A recent experience illustrated the value of immediate reoperation and drainage:

S.S., a 55-year-old man, appeared to be making a gratifying convalescence after gastrectomy. Closure of the duodenal stump had not been difficult. However, signs of duodenal fistula appeared on the 4th postoperative day, confirmed by immediate reoperation. Sump drainage was instituted. Complete recovery followed a stormy convalescence.

A two-stage gastrectomy[32] has been carried out in 2 cases. In 1, catheter duodenostomy still seemed imperative at the second stage because of the degree of persisting induration. McKittrick[33] and Moore[34] continue to employ the two-stage gastrectomy occasionally. A Bancroft operation was carried out once with fatal outcome from subsequent perforation.

Gastrectomy is believed to have been justified in the 22 per cent of patients operated on because of complicated duodenal ulcer. It is anticipated that gastrectomy will be offered to a larger number of patients in the future and at an earlier stage of persisting disease. Removal of 75 per cent of the stomach is still a proper goal for this hospital. Excision of the duodenal ulcer, even when bleeding has occurred, is not imperative if the location of the ulcer and the condition of surrounding tissues suggest a difficult dissection. Vagotomy and gastroenterostomy are probably the best compromise in the occasional difficult ulcer. Catheter duodenostomy is a good safety measure when the surgeon has proceeded with duodenal dissection but at time of closure is confronted with an insecure duodenum or tight closure. The operative mortality was 7 per cent for this fifteen-year period.

Gastrectomy for Gastric Ulcer

Many surgeons express the opinion that gastrectomy should be carried out in almost all patients with a gastric ulceration. They point out the uncertainty of etiology, the high percentage of unsatisfactory response to medical therapy and the greater danger from complications such as perforation and hemorrhage. Welch[16] advises that medical treatment be employed in about 25 per cent of cases. On the other hand, Browne et al.[35] emphasize that fear of carcinoma does not warrant routine gastrectomy. Smith, Boles and Jordan[36] point out that the mortality of 4.8 per cent in patients treated by gastrectomy was greater in a series of 1000 gastric ulcers than that in patients not operated upon (1.7 per cent) and subsequently dying from carcinoma. Experienced surgeons buttress their argument for routine gastrectomy by a mortality rate of 2 per cent or less. The mortality for the entire fifteen-year period at the Salem Hospital was 16 per cent. Although it has been reduced in recent years, the rate is still high enough to restrain enthusiasm for routine surgical intervention on every gastric ulcer.

Table 3. *Indications for Gastrectomy for Gastric Ulcer.*

Indication		No. of Cases
Hemorrhage		29
Persistent gastric ulcer (cancer not suspected)		23
Pyloric obstruction		8
Multiple conditions		1
Stomal ulcer		3
Possible or probable carcinoma		37
Definite x-ray diagnosis of carcinoma	9	
Reasonable suspicion of carcinoma from x-ray and clinical evidence	26	
Diagnosis of carcinoma by gastroscopy done elsewhere	2	
Total		101

An attempt has been made to determine how often gastrectomy should be performed for gastric ulceration; how adequate the hospital's facilities for correct diagnosis are; how many cases of gastric carcinoma have been diagnosed as benign ulcer at some time before operation; whether the equivocal gastric ulcer should be treated by a radical subtotal gastrectomy, a subtotal gastrectomy similar to the operation for duodenal ulcer, or a gastroduodenostomy (Billroth I operation); and, finally, the mortality.

There were 101 gastrectomies for benign gastric ulceration (Table 3). The average age was fifty-six years, with a range of twenty-eight to eighty-three years. There were 68 males and 33 females. During the first half of this study there had been only 21 cases, but in the last seven years 82 gastrectomies have been done. The proportion of patients operated on (about 1 in 5, or 22 per cent) has increased steadily as a natural consequence of greater proficiency and growing concern about the possible presence of carcinoma.

Discussion is warranted with only three groups of cases: bleeding; persistent gastric ulcer in which car-

cinoma is not suspected; and gastric ulceration suspected of being carcinoma. Such a grouping of cases refers to past experience and is not indicative of current apprehension. The possibility of carcinoma must be suspected *in all persistent gastric ulcers* regardless of any combination of apparently favorable factors that formerly may have persuaded physicians to continue nonoperative treatment.

Bleeding Gastric Ulcer

There were 29 patients, 20 men and 9 women (compared with 49 patients bleeding profusely from a duodenal ulcer). The average age was sixty-one, ranging from twenty-eight to eighty-one years. It is recognized that a fatal outcome is more frequent in patients bleeding massively from benign gastric ulcer than in those with hemorrhage from duodenal ulcer.

In only 4 cases was emergency gastrectomy performed because of continuing, rapid blood loss. The feasibility of wedge excision should not be overlooked in the occasional poor-risk patient who might not tolerate a gastrectomy. In 25 cases gastrectomy was carried out at a scheduled time some days after admission. There were 3 postoperative deaths. Autopsy in 2 cases demonstrated massive pulmonary embolus in a sixty-nine-year-old patient and peritonitis from leakage around a jejunostomy tube. The third patient, aged seventy-seven, appeared to have died from pulmonary infarct. There were no deaths in the 4 patients who had emergency gastrectomy; all had been in shock from blood loss either on admission or shortly thereafter, and had had profound hematemesis or melena on the day of emergency operation.

Persistent Gastric Ulcer

There were 16 males and 7 females, with an average age of fifty-two years, ranging from thirty-one to seventy-four. The average duration of symptoms was four and seven-tenths years for men and nine months for women. This shorter period of preoperative observation is probably related to the fact that the female patients were eight years older on an average than the male. There was 1 postoperative death (4.3 per cent).

The danger of making a distinction between a group of patients with persistent gastric ulcer assumed to be benign and a second group, in whom the gastric ulceration is revealed by operation to be carcinoma, is recognized. Few patients with a persisting gastric ulcer would now be treated by a continuing medical program. In many of these cases ulceration had been acknowledged for eight to ten years before operation. Gastric acidity, which had been determined in only 7 cases, was lower than average in 4. Aspiration studies of cytology were performed in only 6 patients. It was concluded from some of these records that the physician in charge was reassured by the coexistence of a duodenal deformity on x-ray study, but it has been pointed out[36] that recognition of such a deformity does not help to differentiate a benign from a malignant *gastric* ulcer.

Probable or Possible Gastric Carcinoma

In 37 patients gastrectomy was performed because of a definite preoperative diagnosis of carcinoma or a reasonable suspicion. In 9 cases a positive diagnosis had been made by x-ray study. In 2 additional cases a preoperative diagnosis of carcinoma was based on gastroscopy without biopsy. In the remaining 26 cases reasonable suspicion was justified by the clinical picture or x-ray findings. The average age was fifty-six years (thirty-four to eighty years). There were 21 males and 15 females. Thus, the surgeon was prompted to perform gastrectomy by his fear of carcinoma in over a third of all gastrectomies for benign gastric ulceration.

The highest operative mortality resulted in this group (7 deaths, or 19 per cent). One of 2 patients operated on because of the gastroscopic diagnosis of carcinoma died of postoperative sepsis secondary to a necrotic ulcer in the bed of the pancreas. One of the 9 patients operated on because of a definite x-ray diagnosis of carcinoma died of pancreatitis after difficult dissection of an adherent prepyloric ulcer from the pancreas. There were 5 deaths among the remaining 26 patients from such causes as stomal obstruction, sepsis and peritonitis (proved to originate from a duodenal leak in 1 case).

Welch[16] states that observation rather than immediate operation is justified in young patients with an acute small ulcer located on the lesser curvature, free hydrochloric acid in the stomach and prompt healing without recurrence on later x-ray study. The danger of reliance on any one of these clinical or x-ray characteristics must be recognized. Neither the size of the ulcer nor its location, whether in the prepyloric region or along the greater curvature, can provide conclusive evidence that it is benign or malignant. Anacidity is a normal state in 10 per cent of men and 14 per cent of women.[37] Low or absent free acid is found in 75 per cent of patients with gastric carcinoma, but about 10 per cent have high acid levels.[38] Nearly 100 per cent of patients with peptic ulcers have normal or elevated levels of hydrochloric acid.[5] Presence of occult blood in the stools is not helpful. Cooper[5] believes that cytologic examination employing the abrasive-balloon technic is at least as accurate as x-ray study. The diagnostic pitfalls encountered in small ulcerations, along the lesser curvature and in young persons are well illustrated in the 2 cases reported below.

G.B., a 47-year-old man, had been studied at another hospital 5 months previously. He gave a 4-year history of indigestion. Initial x-ray study suggested a small benign ulcer on the mid-lesser curvature. Peristalsis was complete along both curvatures. No mucosal destruction was seen (Fig. 3). Gastric analysis was not done. The patient was placed on an ulcer regimen, with only brief improvement. He lost 16 pounds. Repeat x-ray studies 6 months later demonstrated a polypoid carcinoma of the greater curvature.

A thoracoabdominal total gastrectomy combined with splenectomy and resection of two thirds of the pancreas was performed for extensive anaplastic carcinoma. The proximal and distal margins of the resected specimen were free of tumor. Metastases were present however in each of 12 lymph nodes, none of which were obvious at time of operation. The patient was discharged from the hospital in 11 days. He ate surprisingly well, but thereafter failed rapidly and was dead in 11 months.

Although polypoid carcinoma is the most hopeful type of gastric carcinoma this patient had extensive submucosal spread. An initial "test of healing" would probably have led to gastrectomy six months earlier. Some palliation may have been obtained by this otherwise futile, very extensive operative procedure.

R.B., a 36-year-old woman, had been hospitalized at the Salem Hospital 2½ years before gastrectomy because of massive upper gastrointestinal bleeding (admission red-cell count, 2,600,000). X-ray study demonstrated "an indurated gastric ulcer of the lesser curvature several centimeters below the esophagus." X-ray films in August, 1947, showed hypertrophic gastritis with a probable active ulcer at the same location. The report at this time read, "It is necessary to consider this *a benign ulcer.*" The ulcer regimen was continued.

She was readmitted to the hospital 18 months later because of a 2d episode of massive bleeding evidenced by hematemesis and melena. Subtotal gastrectomy was performed in February, 1949, for an extensive anaplastic adenocarcinoma of the stomach, extending to the proximal line of transection on microscopical examination.

Five and a half years after this resection she left perfectly well, had gained weight and was teaching school regularly.

X-ray examination reveals few small carcinomas of the stomach except those along the lesser curvature that resemble benign ulcers.[5] Study of acidity and cytology had not been done. The understandable preoperative diagnosis was "gastric ulcer." It is, of course, very significant for prognosis that no lymph-node metastases were recognized although histologic examination showed anaplasia. Anaplasia is no longer regarded as warranting an inevitable gloomy prognosis. Harvey et al.[39] mention 3 patients apparently cured for over five years in whom the proximal line of transection was carried through the gastric carcinoma.

Concern about correct diagnosis in all gastric ulcerations must be balanced against the mortality rate for gastrectomy in this series. All patients with a gastric ulcer should submit either to immediate operation or to hospitalization. Welch[40] and Schatzki[41] affirm that a ten-day period of hospital medical treatment is sufficient to permit reasonably accurate x-ray reappraisal of the healing tendency in a gastric ulcer. In addition subsequent x-ray examinations are, of course, required to confirm continuance of the progressive healing. Marshall[42] believes that patients should be treated in the hospital for as long as four weeks. At the Lahey Clinic gastrectomy is performed on about 50 per cent of the patients. Cain[43] estimates that, at the Mayo Clinic, immediate gastrectomy is performed in 60 per cent of patients with a gastric ulcer.

In my opinion gastrectomy was indicated in at least 50 per cent of all these patients with a gastric ulcer.* Immediate operation without a "test of healing" would be proposed for the male patient over thirty-five years of age with diminished or absent acidity and an ulcer not located on the lesser curvature. Diagnosis can be improved by insistence on more rigid x-ray surveillance after an appropriate period of hospital treatment in suitable cases. Gastric analyses for acidity and cell study should be done routinely in all gastric ulcers. Gastroscopy would have improved the diagnostic accuracy in this series.

FIGURE 3. *Initial X-Ray Studies Six Months before Operation in Patient G.D., Interpreted as Showing a Small, Benign Ulcer on the Lesser Curvature of the Stomach.*

Nine cases that proved to be gastric carcinoma were diagnosed as benign on x-ray study at this hospital before operation. By comparison a preoperative x-ray diagnosis of carcinoma has also been made in 9 patients who proved to have a benign gastric ulcer microscopically. Both stomach and surrounding gastric bed should be more widely excised in all cases of gastrectomy for gastric ulcer than has been done previously at this hospital.

The mortality rate for this fifteen-year period is 16 per cent. Physiologic arguments make gastroduodenostomy rather than gastrojejunostomy an attractive solution if no compromise in the extent of gastric resection is entailed. Digestion of fat and protein is said to be more complete when the food current passes over the duodenum. The nutritional state of animals after a Billroth II gastrectomy was markedly inferior

*I now believe that a greater number of these patients with gastric ulcer should have a gastrectomy — perhaps 75 per cent.

to that of animals with a Billroth I type of gastrectomy.[44] Harkins[15] and Zollinger[18] both emphasize the value of gastroduodenostomy in the promotion of a better state of nutrition in the postoperative patient. Moore and Harkins are convinced of the superiority of gastroduodenostomy when possible for either gastric or duodenal ulcer and in some cases of gastric carcinoma. However, it has not yet been demonstrated that anastomosis of the short proximal segment of the stomach to the partially fixed duodenum can be done as safely in this hospital as anastomosis to the mobile jejunum. I propose to make guarded use of gastroduodenostomy in selected patients in the future.

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MEDICAL PROGRESS

DERMATOLOGIC THERAPY

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DURING the past few years there have been notable trends in dermatology. As a result of the many new drugs such as the steroids and the antibiotics, which necessitate increased systemic study of the patient and increased laboratory corroboration, there has been close co-operation between all branches of medicine and dermatology. Prevention of cutaneous diseases and rehabilitation of those afflicted is now discussed, and there is evidence of excellent teamwork by those interested in this subject. Lastly, with the large increase in postgraduate study of dermatology, more dermatologists have accepted full-time roles as teachers and research workers. The literature is replete with the results of these investigations. However, since much of the work is as yet only in process and no significant study has been completed, this review is confined to therapy.

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Surgery

Skin abrasion and skin planing in the treatment of blemishes, scars, tattoos and pits due to acne have again extended hope to patients and stimulated the artistic endeavors of plastic surgeons — not to men-

tion some would-be surgeons with little or no surgical training. It is every physician's aim to repair the ravages of disease. There is nothing more distressing to a patient than an ugly scar on the exposed skin, especially the face. He or she will go to extremes to get rid of it.

In the past thirty years I have tried various methods of surgical repair. Years ago the late Dr. F. J. Cotton, a noted sculptor, tried molding fat from the buttocks of patients under old acne scars on the face. The results were disappointing to all concerned. I have sent patients to various excellent plastic surgeons for excision and plastic repair of old acne scars, but I never saw a patient satisfied. They all complained of the results and the costs, although a few results appeared satisfactory to me. In 2 cases there was severe exacerbation of the acne.

Patients with acne tend to form keloids, which may be increased by surgical trauma. Much can be accomplished by slow abrasive methods. Abrasion dates back to antiquity, when an alabaster mixture was mentioned as an abrasive to make the skin smooth. Many types of keratolytics have been used to peel the skin in very young adults, with excellent success. Patients grow impatient under this long process, however, and demand more radical treatment. Since the latter part of the last century, needling, multiple incisions, various chemical caustics and carbon dioxide slush have been tried, without too much success. Sandpapering is losing its popularity, owing to the possibility of silica granuloma from particles of abrasive that become imbedded in the skin.

In 1905 Kromayer[1] introduced skin planing, with virtually the same methods and instruments as those now in use. This procedure was revived by Kurtin[2] in 1952, when he demonstrated refrigeration-abrasive skin planing, using a technic similar to that described in Kromayer's[1] book, published in 1930. In this method the scars are planed by revolving, electrically driven stainless-steel brushes. The width of the brush depends on the size of the scar and of the area to be treated. The brush is placed against the surface of the skin horizontal to the area and moved slowly up and down, causing an abrasion accompanied by considerable bleeding. This sometimes makes it necessary to stop the procedure, but the bleeding is generally controlled with dry sterile gauze, which is usually left on as a dressing.

Despite thirty years of experience with this method, Kromayer never reached the heights of enthusiasm expressed by present-day advocates after only three years' trial. He cautioned that only planing limited to the epidermis and cutis vasculare would heal without scarring, employed his technic only for juvenile warts, freckles and pigmentation, and stated that he had abandoned ethyl chloride anesthesia.[1] I believe that ethyl chloride is a tricky anesthetic and that its limit of safety is very small.

In closing the discussion of their excellent review on dermabrasion, Blau and Rein[3] stress the following points:

> The patient should not be promised too much and, if possible, the end result should be underestimated.
>
> One should be careful in the selection of the patient, with particular attention to the psychologic status and the type of scarring.
>
> Black-and-white photographs of all patients should be taken before therapy; post-therapeutic pictures are not necessary.
>
> The dressings should be removed as soon as possible after dermabrasion.

Eller[4] reports over 200 cases in which he claims excellent cosmetic results by skin abrasions.

Hubler[5] found 1 per cent methylrosaniline chloride (gentian violet) useful for delineating scarred areas before planing. Further experience demonstrated the advantage of painting the entire area to be treated. The rotating wire brush removed the dye with each stroke, showing the exact area treated. Furthermore, the depth of treatment could be judged from the completeness of removal. The wearing of rubber gloves on the left hand of the operator and his assistant helped to protect the fingers from the cold while gauze was being held to confine the ethyl chloride spray during the freezing process. Before the methylrosaniline chloride technic it was necessary to repeat the plastic planing four to six times. Since then good results have been achieved with two treatments.

Rhinophyma, a bulbous disfigurement of the nose, is distressing to any patient. Nevertheless, patients are reluctant to be hospitalized for plastic surgery, although it is usually successful. Niedelman[6] reports an excellent cosmetic result in a case treated by monopolar electroshaving. This can be done in the office, and infections are less likely than with plastic surgery; the method is inexpensive and bloodless and can be performed without interruption of the patient's employment. The cosmetic results are better than or equal to those achieved with plastic surgery.

Kazanjian and Roopenian[7] give an excellent review of their clinical experience in the treatment of hemangiomas. There is no satisfactory conservative therapy for eliminating extensive capillary hemangiomas. In fact the use of cosmetics to conceal such lesions gave better results than surgery, radiation, destruction by carbon dioxide snow, tattooing and other methods. In certain selected cases, however, depending on the size and configuration of the lesion, the area involved and other factors, surgery was used advantageously.

In adult patients with venous hemangioma (strawberry marks) surgery was the method of choice, repair being effected by pedicle flaps from the surrounding healthy skin or by skin grafts, and rarely by flaps transferred from distant areas. In children radiation was successful in reducing the lesion to varying degrees, but later surgery was almost always necessary

to correct the resulting surface deformity. In adults localized cavernous hemangiomas were always treated by surgery. In diffuse types x-ray treatment, sclerosing solutions or electrocoagulation was used to reduce the lesions and make future surgical procedures more simple.

The large earrings worn nowadays require firm fixation to prevent loss, and as a result requests for piercing of ears are increasing. This is a simple procedure. Mandel[8] reports an improved method in which the barbed end of the earring is inserted into the lumens of various hypodermic needles to determine the gauge of the earring. The stylet is placed inside the needle that affords the closest fit, care being taken to keep the bevels in parallel planes. The exact spot to be pierced is indicated by the patient, the lobule is cleansed with thimersol (Merthiolate) and alcohol, and the needle and stylet together are thrust through from the front into a piece of cork held behind the ear lobule. The stylet is then removed, and the barbed end of the earring is inserted into the anterior lumen of the needle. Gentle pressure is applied to the earring and needle, conveying both through the lobule.

Dermatologists have taught for many years that unsightly or easily traumatized pigmented moles should be removed before puberty. Pack and Anglem[9] proposed that malignant melanomas of childhood tend to follow a benign course. It has always been a worry whether or not such lesions were melanomas. However, any tumor in children, as in adults, that is rapidly growing, is ulcerated or shows changes in color and increased pigmentation should arouse suspicion and be excised. So far as growth is concerned most pigmented nevi in childhood become the quiet, harmless intradermal nevi of adulthood. This subject is adequately discussed in a recent report by McWhorter et al.[10] on the treatment of juvenile melanomas and malignant melanomas in children. They state that the juvenile melanoma is a newly identified lesion that appears to be benign and that it can be differentiated histologically from malignant melanoma, with which it has been confused in the past. It comprises 6 to 8 per cent of all pigmented nevi surgically removed from children. It is also seen rarely in adults. Juvenile melanomas should be treated by complete removal, which need not be radically wide. Malignant melanoma occurs in children and may result in metastatic spread and death. It is rare before puberty. It does not differ clinically or histologically from malignant melanoma in adults, and treatment in either should be the same. As wide an excision of the primary lesion as practicable should be undertaken. The resulting defect usually requires a skin graft, after which the patient should be checked frequently for possible involvement of lymph nodes. Regional dissection of lymph nodes is indicated for any nodal enlargement that appears to be metastatic in origin. Routine dissection of nonpalpable regional nodes as a prophylactic procedure is not warranted on the basis of present evidence.

Therapy for Leg Ulcers

Chronic granulating leg ulcers are frequent sights in all large surgical and skin clinics. They are subjects of frequent controversy, and patients are often transferred from one department to another. In thirty years I have tried numerous methods of therapy, with both good and bad results. Perhaps the longest-lasting and most efficient mode of treatment is the gelatin boot, but it requires time and is discomforting, malodorous and frequently unsuccessful. The Unna boot and similar dressings must be worn in bed, adding to the patient's discomfort. Reisch and Combes[11] suggest a new type of pressure dressing — namely, the foam-rubber boot. This can be made from a sheet of rubber, adhesive tape and a zipper. During the day it maintains uniform pressure from ankle to knee, and by means of the zipper it can be removed at bedtime or for changing of dressings. As the edema subsides, the legging is shaped by minor adjustment to conform with the new configuration of the leg.

The treatment of leg ulcers with antiseptic powders has been tried since antiquity. Although it is successful in a certain percentage of cases, the poor results in others, because of untoward reactions of sensitivity, usually discount the good results. At one time Furacin-soluble dressing seemed to be the answer, but the rapid sensitization action of the compound soon became apparent, preventing its continued use.

Robinson[12] reports successful treatment of 72 patients with leg ulcers by antibiotics. Dermatitis developed in 7 patients — in 4 from chloramphenicol. This percentage of nearly 10 per cent sensitization is too high a risk for any therapy.

Enzymic débridement is not new, having been in use many years ago at the Boston City Hospital. The problem of infection was difficult to control, but today, with the antibiotics available, a combination with enzymes seems a logical one. Spier and Cliffton[13] report successful results from a combination of hyaluronidase, plasminogen and antibiotics in 16 patients with chronic ulcer who had been treated by routine methods for long periods without success.

Milberg and Tolmach[14] describe healing of leg ulcers in 86 cases and improvement in 11 through the use of sterile absorbable gelatin sponge in powdered form. The procedure consisted of packing the ulcers with the powder, covering with dry gauze and applying an Elastoplast dressing or elastic bandage. The patients were instructed to leave the dressing in place and return in a week. When infection was present, powdered oxytetracycline or chlortetracycline was put in the ulcers before they were packed. Milberg and Tolmach also spread a soothing paste such as zinc oxide over the areas of dermatitis before applying the fixed dressing. Failing to take the latter simple step has made it necessary to discontinue many types of fixed dressings because a mild dermatitis increases, with disastrous results, unless the surrounding edge of the ulcer is protected from irritation.

Patch Tests

The best cure for a persistent or recurrent contact dermatitis is to find the causative agent and to have the patient avoid contact with it or with chemically related matter. The patient usually recognizes a primary irritant, but the situation is not so simple when the agent is a sensitizer, since he may have been in contact with this material for years before becoming sensitized to it. Therefore, a careful history should be taken to reveal the possible allergens, with which the patient should then be given patch tests.

Fernstrom[15] believes that the patch-test procedure generally used, here called the routine method, does not invariably fulfill essential conditions. It fails to prevent a change in the position of the patch during the period of exposure, so that the allergen does not invariably act on the same area of the skin. Imperfect contact between skin and patch cannot always be ruled out. In addition the routine method is ineffective in producing an occlusive chamber around the patch to avoid evaporation.

For this reason a new patch-test technic was evolved. The patch is a square of blotting paper or lint, 8 by 8 mm., covered with a square of rubber, cloth or cellophane, 21 by 21 mm., on which a block of sponge plastic or sponge rubber, 19 by 19 by 4 mm., is placed. Patch, waterproof cover and block of elastic material constitute one unit. The patches are moistened with the allergen solutions, and the units are attached to the skin with tape. The elastic material, being compressed during application, will subsequently maintain continuous pressure against the skin. The patches will thus remain in close contact with the initial contact site of the skin, and the waterproof covers will produce satisfactory occlusion. Since the pressure due to the resilience of sponge plastic is the essential detail of the new test technic it is called the "pressure patch test." With this technic fewer cases of sensitivity are apt to defy detection. In 121 cases with established sensitivity, tests were made simultaneously with both methods. In 19 the routine method failed when there was response to the pressure patch test. The reverse was noted twice.

Antihistamines

Antihistamines have been a great disappointment in the treatment of cutaneous sensitivities. In urticaria, acute or chronic, they may give temporary relief. Some have a sedative effect, which is of some value in the extremely pruritic patient, but they rarely relieve pruritus — nor do they check the eruption. Their extensive use produces side effects and causes allergic reactions in the form of drug eruptions.

The antihistamines have been applied locally in many dermatologic entities, ranging from fungous infections to scleroderma. These drugs are local anesthetics but are also irritants and sensitizers. At its annual meeting in 1952, the Council on Pharmacy and Chemistry of the American Medical Association[16] voted to discontinue the acceptance of topical dermatologic preparations of all antihistaminic drugs. It concluded that, although some of them apparently have been helpful in relieving certain types of pruritus, the risk of contact dermatitis now overshadows their possible efficacy for that purpose and that further evidence is required to establish their usefulness. I have seen more serious sensitizing reactions from Caladryl (the calamine lotion containing Benadryl Hydrochloride) and Thephorin (phenindamine tartrate) than from any other two local applications.

Antibiotics

The antibiotics provide powerful weapons against the various pyodermas. Careful selection of the one suitable for the existing infection is necessary. Penicillin is still the most efficient and economical antibiotic for most susceptible infections. Like the sulfonamides, it should not be used topically because of its allergenicity. It causes severe reactions in a large number of people. Boger et al.[17] state that anaphylaxis occurs only in patients who have been previously sensitized, develops most commonly in those who have shown previous sensitivity phenomena and is observed rarely, if at all, with oral usage. The shocking dose is generally the first one to be given after a long interval since previous exposure. Intracutaneous skin testing is of value, but a negative reaction can be followed by a serious reaction. Hypoallergic penicillin "o," "compenamine" and "BT" may be useful in certain patients with reactions or known to be hypersensitive to either soluble penicillin G or procaine penicillin, but may also cause reactions. Many new penicillin preparations represent a chemical union of two drugs. With these, potentials of sensitization are increased. Adrenalin, ACTH, cortisone, hydrocortone, and antihistamines are suggested for the treatment of penicillin reactions. ACTH acts faster and is more physiologic than cortisone.

Herrell[18] cites the reaction of toxicity to other antibiotics. Chloramphenicol may suppress the bone marrow, producing severe leukopenia. Fatal aplastic anemia may result from the use of this drug. Chlortetracycline and oxytetracycline cause nausea, vomiting and severe colitis. When staphylococci are present with diarrhea erythromycin therapy will usually eliminate the illness. Perirectal and vaginal irritation, with pruritus, are often seen with chlortetracycline and oxytetracycline. The removal of the bacterial flora and replacement by a fungous flora will often result in a glossitis. Cutaneous reactions have been low with these antibiotics. Rashes have occurred, as has urticaria. Neomycin administered parenterally has produced involvement of the eighth cranial nerve and renal irritation. Bacitracin given parenterally may also cause renal irritation. Polymyxin should be used parenterally only in infection caused by *Pseudomonas aeruginosa*. This is a severe neurotoxin. Paresthesias and cerebellar ataxia may occur.

At present neomycin, bacitracin and polymyxin, being limited in systemic use, should be the topical antibiotics of choice. Neomycin has a broad spectrum and a low sensitizing index and is soluble and stable in solution. It is useful as a compress or in an ointment, but it is inferior to oxytetracycline for infections with the hemolytic streptococcus. Bacitracin affects most of the bacteria destroyed by penicillin, especially the streptococci, and polymyxin attacks infections due to *Ps. aeruginosa*.

Infections due to *Ps. aeruginosa* and *Proteus vulgaris* are rapidly increasing because of the prolonged use of antibiotics. More cases of cutaneous moniliasis are being seen. An antibiotic locally applied should have accomplished its purpose in seven to ten days and should then be stopped, or replaced by another if the skin is not cleared.

Tetracycline seems efficacious in rapidly spreading cutaneous infections such as furuncles and carbuncles, and causes less gastrointestinal disturbances. Despite the frequent admonition not to use a drug locally that may later be invaluable in serious systemic infections, physicians continue to employ all the antibiotics locally. Tetracycline administered systemically rapidly controls the secondary infection commonly found in contact and industrial dermatitides.

Erythromycin has been used extensively in the treatment of dermatoses. Robinson and his associates[19] administered the drug orally to 681 patients and topically to 1014. Erythromycin in enteric-coated tablets proved to be of definite benefit in the treatment of all conditions in which pyogenic organisms were the primary cause of the disease. Oral administration was also of value in the eradication of secondary pyogenic infection from dermatoses such as atopic dermatitis, epidermophytosis and seborrheic dermatitis, but had no beneficial effect on the primary disease. Rapid involution of lesions of granuloma inguinale followed the institution of therapy. This drug also proved to be of value in the treatment of erythema multiforme. Erythromycin may be considered an adjunct to the therapy of acne vulgaris, but it does not replace any of the standard methods of treatment in use at present.

Robinson[20] also summarizes the role of antibiotics in the therapy of acne. He concludes that the broad-spectrum antibiotics have value as supplementary therapy and do not replace x-ray therapy, dietary measures and proper local treatment. They should not be used locally because they may cause acquired contact sensitivity. Penicillin by injection is of no value. Oxytetracycline, chlortetracycline and erythromycin are the drugs of first choice. Chloramphenicol is not recommended because of the possible production of blood dyscrasias. Rest periods are advisable, and improvement may be maintained in a high percentage of cases by administration of subtherapeutic maintenance doses.

Van de Erve[21] tried erythromycin in 60 cases of acne vulgaris of various types, with excellent control of the pustular element in nearly all. This improvement was temporary, with recurrence in the majority of cases within a month of treatment. There was little or no effect on the sebaceous secretion itself, either in the formation of oil on the skin or as comedones. Only 1 patient was intolerant of the drug, manifesting diarrhea to the extent of having to discontinue therapy. No untoward effects such as monilial overgrowth and disturbance in the bacterial balance were noted. The drug is apparently safe and is valuable for the control of the pustular phase of acne vulgaris but has little effect on the basic sebaceous overactivity. In my opinion antibiotics should rarely be used in acne vulgaris; besides being of only temporary value they make the condition more refractory to treatment.

A recent editorial[22] gives an excellent résumé on the value of erythromycin. It emphasizes the fact that erythromcyin, like other antibiotics, should not be given except with clear indications and states that the possible development of resistant staphylococci during its administration should always be borne in mind, irrespective of the nature of the infection under treatment. Prolonged use of erythromycin alone should be avoided under all circumstances.

Carbomycin (Magnamycin) was used in the treatment of granuloma inguinale by Robinson and Cohen,[23] with the following results. Six patients were given enteric-coated tablets, 1 receiving 200 mg. every six hours, 1 receiving 250 mg. every six hours, and 4 receiving 300 mg. every six hours. All 6 patients had satisfactory results, with complete healing of the lesions, and no relapses were noted in a follow-up period of one to three months.

Burke et al.[24] report on a new antifungal antibiotic, Mycoticin, which has been isolated in crystalline form from *Streptomyces ruber*. It is particularly active in vitro against *Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis, Sporotrichum schenckii,* and *Microsporum audouini*. The probable chemical formula is $C_{18}H_{35}O_5$. This antibiotic has several interesting features, including ability to fluoresce under ultraviolet rays, a property that can be roughly correlated with activity. The crystalline material rapidly becomes inactivated unless stored in a vacuum. A fairly accurate estimation of antifungal activity can be determined by ultraviolet spectrum. Toxicity is quite high, the approximate LD_{50} being between 10 and 20 mg. per kilogram of body weight when the drug is administered intraperitoneally to mice. Hemolysis was not evident in the autopsied animals.

Steroids

Cortisone and ACTH have been used fairly extensively in large clinics in the treatment of many cutaneous afflictions, ranging from acute dermatitis venenata to scleroderma. After six years of trial and error their value and limitations are now fairly well recognized. Intramuscular injection of 100 to 150 mg. of ACTH

per day for a short time, followed by a daily dose of 200 mg. of cortisone, will suffice in most cases. Occasionally, larger doses are necessary. One patient with severe pemphigus for two years has continued his occupation on a maintenance dose of 100 mg. per day.

The main trouble with these drugs is the risk attendant on their sudden discontinuance; they must be withdrawn slowly and cautiously. The serious complications are well known. It has been stressed[25] that in the majority of patients the prolonged use or excessive dosage of ACTH, cortisone and hydrocortisone may produce undesirable side effects, which, however, tend to disappear when the treatment is discontinued. It is to be remembered, nevertheless, that the unfavorable sequelae may appear six months after the drug has been stopped, and this delayed reaction may be serious. It has recently been emphasized that if a patient has been receiving one of the steroids and its use is discontinued, and the patient is then found to require a surgical procedure for some condition unrelated to that for which the steroid originally was given, it is necessary to give the cortisone and ACTH again before and after the operation. In deaths that followed surgery after cortisone had been given for several months, pronounced atrophy of the adrenal glands was found. Anyone who has received cortisone or ACTH within six months of a contemplated operation and who is to undergo the trauma of surgery, or who has sustained an accident within that period, should immediately be given one or the other of the steroids again. It has even been suggested that patients who have had treatment with either drug carry a card indicating the fact that they have had such treatment, and the amount of the drug given, so that in case of an emergency, steroid treatment may be resumed without delay.

Welsh and Ede[26] treated 402 patients with the following preparations: hydrocortisone (Cortril), acetate topical ointment and hydrocortisone (Cortril), free alcohol topical ointment, 1 per cent and 2.5 per cent concentrations (10 mg. and 25 mg. per gram, respectively). They concluded that hydrocortisone alone may give dramatic temporary results but that, combined with conventional preventive and therapeutic procedures it can be a most valuable adjunctive measure for dermatologic use. Alone, hydrocortisone is an effective therapeutic agent only in acute contact dermatitis, in mild transient exacerbations of atopic dermatitis or infantile eczema, in uncomplicated stasis dermatitis and in some cases of idiopathic pruritus vulvae or pruritus ani or both. In long-standing atopic dermatitis, chronic contact dermatitis and localized neurodermatitis with lichenification, hydrocortisone is an inadequate therapeutic agent when used alone, but it is a valuable adjunct when combined with other antieczematous topical and systemic agents. The free alcohol ointment appears to be more effective than the acetate ointment.

9α-fluorhydrocortisone acetate, a derivative of hydrocortisone, was used to treat 51 patients with dermatoses reported as amenable to topical hydrocortisone acetate and hydrocortisone free alcohol therapy, such as atopic dermatitis, allergic eczematous contact dermatitis, nummular eczema and lichen simplex chronicus. In 28 cases the side of the body treated with fluorhydrocortisone acetate appeared to be more improved than the side treated with hydrocortisone free alcohol, and in 8 of these cases the difference in favor of the fluorhydrocortisone was very distinct. In 16 cases the two compounds were equally effective; in 2 cases they were both ineffective, and in 5 fluorhydrocortisone acetate was less effective than hydrocortisone free alcohol. The results here reported suggest that 9α-fluorhydrocortisone acetate is slightly more effective than hydrocortisone free alcohol in the topical therapy of the majority of the selected dermatoses treated.[27]

Hormones

The eternal feminine struggle to maintain beauty has made the cosmetic industry a billion-dollar business. To "retain that schoolgirl complexion," some firms have suggested that hormone creams will delay the aging process of the skin, rejuvenate and prevent wrinkles.

To demonstrate the effects of estrogenic hormone cream on facial skin, Behrman[28] tested a group of 31 women (4 of whom did not complete the test and were not included in his report), all over thirty-five and up to sixty-five years in age. They were selected on a basis of intelligence and faithfulness to testing procedures, as indicated by their records of performance in similar procedures. Detailed background data on age, menstrual history and cosmetic habits were recorded. The only clinical changes observed from both subjective and objective standpoints consisted of a lessened degree of dryness in facial skin that was previously of an asteatotic or dry type. No appreciable difference was visually observed in the side treated with an estrogenic hormone cream as compared with the side treated with either the identical base without hormones or a commercial night cream having a composition similar to that of the hormone cream. This study demonstrated that noticeable improvement in the appearance of the skin can be obtained through regular use of an emollient cream on women with dry skins. It did not demonstrate that the addition of hormones to such emollient bases increases this improvement to any discernible extent.

Peck et al.[29] present laboratory and clinical data on the efficacy of a lotion that combines keratolytic, antibacterial and estrogenic principles for the treatment of acne vulgaris. Good to excellent immediate results were obtained in 55 of 69 cases studied. Apparently, the topical application of estrogenic hormones (50,000 international units per ounce) played a significant part in controlling the recurrences, presumably by decreasing the activity of the sebaceous glands; the remaining components of the lotion appeared to influence the other manifestations of acne lesions already

present. There was no evidence of any systemic effect from the daily application of 50,000 international units of estrogen per ounce of this lotion used for a period of one month. The lotion seemed to have a somewhat better effect on males than on females.

Shapiro[30] tried a lotion containing 2.5 mg. of conjugated estrogens (equine) per cubic centimeter. Seventy per cent of cases refractory to other forms of therapy responded to topically applied natural estrogens. A lotion of conjugated estrogens (equine) has several advantages: high local concentration of estrogen, flexibility of dosage control, no unwanted side effects with correctly adjusted dosage schedule, acceptability to both sexes, compatibility with other therapy and high effectiveness.

Newman and Feldman[31] treated 95 women between twenty and fifty-one years of age for adult premenstrual acne. Sixty-two had received complete x-ray therapy. In addition, ultraviolet radiation, vitamin A, estrogens and dietary restriction had proved unsuccessful. The patients were classified in three main groups: those with lesions appearing for the first time after the age of twenty; those with premenstrual eruptions and the usual comedones of acne vulgaris beginning concomitantly in adult life; and those with adolescent acne vulgaris persisting into adulthood. These investigators proceeded on the thesis that premenstrual acne may be caused by corpus-luteum deficiency. Ten milligrams of progesterone (10 mg. per cubic centimeter of sesame oil) was injected intragluteally ten days before menstruation; 5 mg. was given five days before menstrual onset. If the injections inhibited premenstrual acne 10 mg. of progesterone buccal tablets was then administered daily for ten days before the menses. The period of therapy varied from five to twenty months.

Eruptions were completely inhibited by progesterone therapy in all the 36 patients in the first group. Lesions of half the patients disappeared with buccal tablets. In the second group comedoacne resolved in 14 of 15 patients after x-ray therapy, but noncomedopremenstrual lesions remained unchanged until progesterone was given. In the third group only 2 of 44 women had premenstrual acne after hormone treatment; 1 of the 2 experienced an exacerbation during therapy. Progesterone is not effective for controlling flare-ups of the usual acne vulgaris or for patients without definite premenstrual exacerbations.[21]

(To be concluded)

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MEDICAL INTELLIGENCE

ADRENAL APOPLEXY FOLLOWING ELECTRONARCOSIS THERAPY*

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WAVERLEY AND BOSTON, MASSACHUSETTS

A RECENT review of the subject of adrenal apoplexy[1] listed convulsions among the causes of that syndrome. It is known that massive adrenal hemorrhage occurs in occasional patients with severe epilepsy; indeed, this lesion may even be the cause of death in status epilepticus.[2,3] In a psychotic patient studied at this hospital adrenal apoplexy developed in association with prolonged induced seizures; it was therefore considered of interest to review available information on the relation of convulsions to adrenal hemorrhage.

CASE REPORT

H. T. H., a native-born spinster, first entered the McLean Hospital in August, 1945, at the age of 73, with a diagnosis of involutional psychosis. Her family history revealed epilepsy and psychoses in several relatives; a brother had schizophrenia. The patient had had no remarkable illnesses until the age of 55, when she became agitated and depressed. At that time she was hospitalized for 4 months, recovering with no specific treatment. Eighteen years later her symptoms returned, and she spent 3 months at another sanatorium. She then came to the McLean Hospital for the 1st of 3 admissions; on this occasion the final diagnosis was manic-depressive psychosis, depressed phase. Laboratory examination revealed that the blood hemoglobin, sugar and nonprotein nitrogen levels were all normal; the Wassermann reaction was negative, and an electrocardiogram was normal. She was given 16 electroshocks in the first 3 months after admission and was discharged improved. Improvement was maintained for 6 months, after which she re-entered the hospital for 15 more treatments over a 3-month period. Again improvement lasted for about 6 months, to be followed once more by relapse. Readmission was followed by the administration of 14 electroshocks over a 4-month period, with moderate temporary improvement. In all the electroshock treatments given the duration of the seizures was between 30 and 45 seconds. Six months later electronarcosis therapy was started; in these treatments the duration of the seizures was between 15 and 25 minutes. Approximately 60 hours after the 6th treatment a nurse found her pale, cold and gasping for breath. She died about 20 minutes later.

Post-mortem examination revealed that the combined weight of the 2 adrenal glands was 24 gm. (about twice the normal weight); the left adrenal gland was enlarged, and the cortex was massively infiltrated with blood. The other gross findings comprised pulmonary edema, a fresh thrombus in a narrowed portion of the left circumflex coronary artery, generalized arteriosclerosis, leiomyomas of the stomach and uterus, and a thickened gall bladder containing many stones. The weights of the heart and lungs were respectively 300 and 1000 gm.

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Microscopical examination confirmed the gross findings and showed, in addition, severe renal arteriosclerosis and also diffuse patchy cerebral nerve-cell degeneration and gliosis; several old healed infarcts were found in the lenticular nuclei.

DISCUSSION

In 1916 Zimmerman,[4] using Dunger's direct method for counting eosinophils, observed eosinopenia after spontaneous epileptic seizures; this finding is now recognized as suggestive of activation of the adrenal cortex. The fact that the adrenal cortex is stimulated during electrically induced convulsions in man is more fully documented.[5] Some types of seizures have been shown to stimulate the adrenal cortex in animals also.[6] It is known that adrenal hemorrhage may occur in patients receiving ACTH.[7,8]

The mechanism responsible for massive adrenal hemorrhage in severe epilepsy is not established; it is worthy of note that the epileptic patients who are reported to have had adrenal apoplexy were among those who had frequent severe convulsions. In the patient described above, the adrenal lesion developed after an electronarcosis treatment, the duration of which was far greater than that of any of the 45 ordinary electroshock treatments that she had received without injury. (Seizures induced in ordinary electroshock therapy last for about thirty or forty-five seconds, as contrasted with those lasting fifteen to thirty minutes that characterize electronarcosis treatments.) Perhaps the unusual duration of the stress of the induced seizure was an important causative factor in the adrenal apoplexy.

The incidental post-mortem finding of a fresh thrombus in a narrowed coronary artery is not rare in elderly patients who have died of any type of shock; in this case the histologic appearance of the hemorrhagic area showed that the hemorrhage had occurred at some time before the thrombus developed.

SUMMARY

A patient who had previously received 45 electroshock treatments without injury died after her sixth electronarcosis treatment; massive adrenal hemorrhage was found at autopsy. The possible relation between adrenal apoplexy and the severe, prolonged stress of convulsions is discussed.

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DOCTORS AFIELD

The Smith Brothers

JAMES F. BALLARD*

BOSTON

ALBERT Richard Smith and Arthur W. W. Smith were the uninhibited sons of an English surgeon. Albert, the elder and better known as a physician, author, traveler, lecturer and entertainer, was born at Chertsey, Surrey, on May 24, 1816. He was educated at Merchants Taylors' School during the years 1826-1831.

At an early age he became interested in medicine and studied at the Middlesex Hospital in London, becoming in 1838 a licentiate of the Society of Apothecaries and a member of the College of Surgeons. In the same year he entered practice with his father at Chertsey. On January 4, 1840, he began his literary pursuits by contributing to the *Medical Times,* writing under the pseudonym "Rocker," a series of articles, entitled "The Confessions of Jasper Buddle, a Dissecting Room Porter."

In 1841 he moved to London and settled at 14 Percy Street, Tottenham Court Road. He had in mind to continue the practice of medicine but was soon diverted by his literary inclinations, showing exceptional versatility in using to account his powers of humorous observation.

In March, 1841, *Bentley's Miscellany* had published his article, "A Rencontre with the Brigands." He was an early contributor to *Punch,* in the October 2, 1841, issue of which his "Physiology of the Medical Student" and on January 1, 1842, "Physiology of London Evening Parties" appeared.

He became interested in drama, his first play, "Blanch Heriot," being produced at the Surrey Theatre on September 26, 1842. Between 1844 and 1846 he wrote, in conjunction with other persons, several extravaganzas for the Lyceum Theatre. The series included "Aladdin," appearing in August, 1844; "Valentine and Orson," in December of that year; and "Whittington and His Cat," in the spring of 1845. Their success was attributed largely to the acting of Mr. and Mrs. Keetley. He also adapted for the Lyceum "The Cricket on the Hearth," produced in December, 1845, and the "Battle of Life," which made its appearance a year later. For the Adelphi Theatre he wrote "Esmeralda," a burlesque, produced on June 3, 1850, and for the Princess Theatre "Alhambra," an extravaganza, produced on April 21, 1851. During this period he acted as dramatic critic for the *Illustrated London News.* He wrote many popular songs for John Orlando Parry.

In 1842 he began, in *Bentley's Miscellany,* "The Adventures of Mr. Ledbury," his most successful novel. He was also an editor, conducting *Puck* in 1844, five issues of the *Town and Country Miscellany,* from April to August, 1850, and in 1851, from July to December, the *Month,* with Leech's illustrations. In 1849 he had edited "Gavarni in London," republished as "Sketches of London Life and Character" in 1859.

In 1847, in conjunction with David Bogue, the publisher, Smith began a series of social natural histories, to be sold at 1 shilling each. They were to be patterned after the style of the Paris physiologies. The first, *The Natural History of the Gent,* was so successful that the first edition of 2000 copies was sold out on publication day. In 1847, in association with Angus Bethune Reach, a publisher, he brought out a 6-penny monthly, *The Man in the Moon,* with which he was connected until 1849.

His satiric essays, which were illustrated by the famous caricaturists, John Leech, Crowquill, Kenny Meadows and H. K. Browne, began with "Beauty and the Beast," which ran from 1843 to 1855, and included "English Hotel Nuisance." In 1856 he presented "Sketches of the Day," in two series.

In 1849 Smith began the third phase of his versatile life as traveler, lecturer and entertainer. In that year he went on a tour to Constantinople and the East. On his return in 1850 he published a book on his travels, *A Month at Constantinople.* On May 28, 1850, he appeared for the first time as an entertainer at Willis's rooms with a show written by himself, "The Overland Mail." On August 12, 1851, he made the ascent of Mont Blanc publicized by Arthur in the following year, and in March, 1852, produced at the Egyptian Hall in Piccadilly popular entertainment descriptive of the ascent and of Anglo-continental life in general. From that time until July 6, 1858, he continued at the Egyptian Hall his career as a public entertainer, presenting new sketches of character but always keeping Mont Blanc as the central point of attraction. On August 24, 1854, he gave a performance before the queen and the prince consort at Osborne House. In July, 1858, he left for Hong Kong, writing "To China and Back" on his return in 1859. This trip was the basis for his new show "China," which also achieved considerable popularity.

His last appearance at Egyptian Hall was on Saturday, May 18, 1859. On August 1 of the same year he married Mary Lucy Keeley, a former actress, the elder daughter of Robert Keeley, the comedian. He died of bronchitis on May 23, 1860.

Arthur W. W. Smith, born in 1825, first broke the sound barrier in 1852 with his work, "A Handbook of Mr. Albert Smith's Ascent of Mont Blanc," which went through 4 editions. He then abandoned a promising medical career to take full charge of the management of his brother's entertainments. In 1858 he directed and managed the readings of Charles Dickens and in the same year edited the *Mont Blanc Gazette.* In 1861, the year of his death, he wrote a brochure, *The Thames Angler,* and edited the *London Medical Student,* first proposed by his brother.

*Deceased; formerly, director, Boston Medical Library.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41311

PRESENTATION OF CASE*

First admission. A forty-seven-year-old man entered the hospital because of recurrent fever of one month's duration.

Six weeks before admission the patient received a tick bite on the right ankle, which he continued to pick at and which produced a crusted lesion. He denied any swelling, redness or adenopathy. Four weeks before admission malaise, throbbing supraorbital headache, a temperature up to 101°F., a dry, nonproductive cough and aching in the lymph nodes of the neck, without sore throat or coryza, developed. The patient took tetracycline hydrochloride (Achromycin) for four days, with some improvement, but three days later he again felt ill, was febrile with a temperature of 101°F. and had tender "glands" in the left side of the neck. Tetracycline hydrochloride therapy was reinstituted for four more days, after which he felt tired and weak. Three days before admission aches in the arms and legs developed, and the next day he had a shaking chill with a temperature up to 103°F. Tetracycline hydrochloride was again started. On the day before admission he had a sharp, steady pain in the lower dorsal and upper lumbar spine, nausea and five watery brown stools. The dry cough, which appeared with the onset of the present illness, had persisted without abatement.

Four years before admission the patient was admitted to another hospital for seven weeks with an anterior myocardial infarction. A chest film showed slight enlargement of the heart in the region of the left ventricle, with a cardiothoracic ratio of 15.4:30.0 cm. At this time nausea, vomiting, diarrhea and a similar low-back pain were present. He was given chlortetracycline (Aureomycin) for pleurisy of the left lower lobe. In the following year he had pneumonia twice. He was subject to frequent respiratory infections, for which he usually received antibiotics, apparently with benefit. One year before admission he was in the hospital for Horton's cephalalgia. At that time an electrocardiogram showed normal rhythm at a rate of 65, a PR interval of 0.20 second, a QRS interval of 0.09 second, broad notched P waves and prominent Q waves in Leads 1 and aVL, and absent R waves in Leads V_1 through V_5; the T waves were inverted in Leads 1, 2 and aVL, with late inversion in Leads V_3, V_4, V_5 and V_6, upright in Leads V_1 and V_2 and low and upright in Leads 3 and aVF.

Physical examination at the present admission revealed a moderately pale man with a dry, intermittent cough. Examination of the skin, head, neck and lungs was negative. The heart extended 9 cm. from the midsternal line in the fifth intercostal space; no murmurs, thrills, or rubs were found; a distinct systolic gallop was heard over the entire precordium, best at the apex. The abdomen and genitalia were normal. There was a 4-mm., crusted, nontender lesion on the right ankle. Neurologic examination was negative.

The temperature was 100.4°F., the pulse 100, and the respirations 18. The blood pressure was 120 systolic, 70 diastolic.

Examination of the urine was negative. Examination of the blood revealed a hemoglobin of 14.0 gm. per 100 cc. and a white-cell count of 12,300, with 81 per cent neutrophils. The erythrocyte sedimentation rate was 44 mm. in sixty minutes, and the cold-agglutinin titer was 1:1. A blood culture, a thioglycolate culture of the blood for leptospira and a Hinton test were negative. A throat culture yielded abundant alpha-hemolytic streptococci and *Neisseria catarrhalis*. A stool culture was negative for enteric pathogens. An electrocardiogram showed a normal rhythm at a rate of 100, a PR interval of 0.16 second, left-axis deviation, broad Q waves in Lead 1 and absent R waves in Leads V_1 through V_5. The T waves were upright in Leads 3, aVF, V_1, V_2 and V_3, diphasic in Lead 2 and inverted in Leads aVL, V_4, V_5 and V_6. The ST segments were elevated in Leads V_1 through V_6. The findings were interpreted as indicating a large anterior myocardial infarct. The elevated ST segments were suggestive of a recent infarct, although they were also consistent with a ventricular aneurysm in a healed infarct (Fig. 1). A roentgenogram of the chest was normal, although there was slight fullness of the left ventricle.

On the second day the temperature, which had risen to 104°F. with a chill on the night of admission, declined to 100°F. Therapy consisted only of salicylates and diphenhydramine hydrochloride (Benadryl). Thick and thin smears revealed no malarial parasites. On the fourth day a patchy gray exudate was noted on a diffusely reddened pharyn-

*Presented at the meeting of the American College of Physicians in Philadelphia, April 26, 1955.

geal mucosa. A throat culture yielded a moderate growth of alpha-hemolytic streptococci and a few diphtheroids, but was negative for *Corynebacterium diphtheriae*. The temperature remained elevated to levels around 102°F. The white-cell count was 16,400, with 83 per cent neutrophils. The bilirubin was 0.6 mg., the total protein 6.8 gm., the albumin 4.2 gm. and the globulin 2.6 gm. per 100 cc.; cephalin flocculation was ++ in twenty-four and forty-

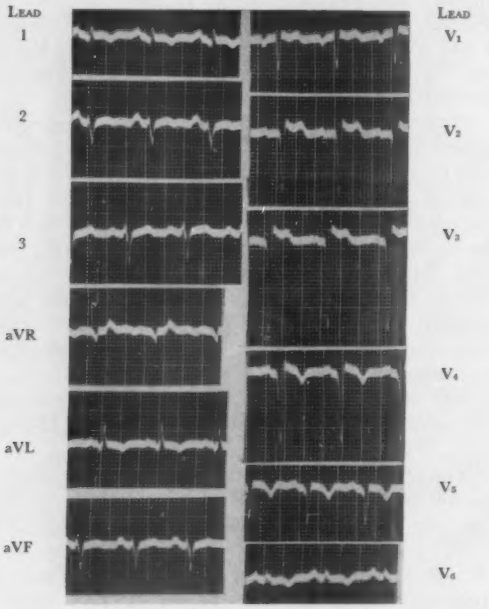

Figure 1.

eight hours. The temperature continued to range between 100 and 104°F., and on the eighth day the patient had a shaking chill. After this episode he complained of soreness across the chest and in the left shoulder. The white-cell count was 17,400, with 77 per cent neutrophils. On the tenth day an x-ray film of the chest showed prominent peripheral vascular markings in both lower-lung fields, with some transverse linear markings. The heart showed some further enlargement in the region of the left ventricle, and the cardiothoracic ratio was 16.5:30.5 (Fig. 2); on the first film the cardiothoracic ratio was 14.5:30.5. An intravenous pyelogram on the same day was normal. During the next two weeks the temperature ranged between 99 and 101°F., with occasional chills. One of the chills was accompanied by tenderness over the fifth rib in the left anterior axillary line. The sedimentation rate was 51 mm. in sixty minutes. The heart was slightly larger to percussion than it had been, and there was evidence of slight pulmonary congestion. A barium-enema examination revealed diverticulosis. After the temperature had remained around 99°F. for several days he was discharged three and a half weeks after entry. During this admission he had received merely supportive treatment; antibiotics were not used because he had received a great deal before admission without much benefit and because it might mask the diagnosis.

Final admission (eleven days later). After discharge, the patient was fairly well for six days with a temperature around 99°F., but then the daily temperature spikes, usually to 101°F., but on one occasion to 103.6°F., returned. Four days before readmission a pressing pain developed beneath the left scapula. During the four days before admission he had a dull headache and felt nauseated; he was constipated until the night preceding admission, when he passed five or six watery brown stools, which contained no gross blood.

On physical examination the skin was warm and slightly moist. Diaphragmatic excursion was de-

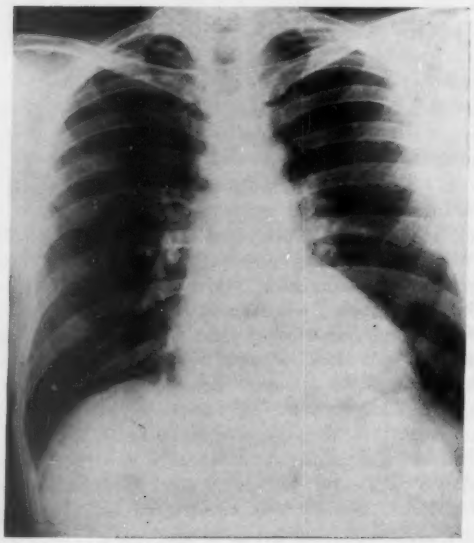

Figure 2. *Posteroanterior Roentgenogram of the Chest. The left ventricle is prominent, and a slight increase in the transverse cardiac dimension has appeared since the films taken ten days previously.*

creased on the left side; dullness, decreased breath sounds and scattered fine dry rales were noted at the left-lung base. The heart extended to the midclavicular line in the fifth left intercostal space. No murmurs, thrills, or rubs were found. The rhythm was regular, the rate was rapid, and the mitral first sound was split. The abdomen, genitalia and extremities were normal.

The temperature was 101.6°F., the pulse 112, and the respirations 20. The blood pressure was 112 systolic, 72 diastolic.

Except for a ++ test for albumin urinalysis was negative. The hemoglobin was 10.7 gm. per 100 cc., and the white-cell count 39,400, with 98 per cent neutrophils. The sedimentation rate was 54 mm. in

sixty minutes. Although an x-ray film of the chest was taken in expiration, in the lateral view a hazy mottled density was apparent posteriorly in one or both of the lower lobes. The left leaf of the diaphragm was very indistinctly seen, and there was a small amount of free fluid in the left pleural space. There was an over-all increase in pulmonary markings. It was believed that the heart had not changed since the films on the previous admission.

The patient's status was unchanged until the morning of the second day when he was found unconscious on the floor after he had tried to use the urinal. The pulse and respirations were rapid; he was very cyanotic; the blood pressure was maintained at 118 systolic, 80 diastolic. Initially, he was unresponsive, with bilateral sustained ankle clonus. Oxygen was given by nasal catheter. One hour later he was in a confused, shouting unco-operative state, and the ankle clonus had disappeared. The heart sounds at this time were of poor quality. He began having brief, shaking chills of a few seconds' duration. The temperature was 103.8°F. by rectum; the pulse was 160, but regular. The chest findings were unchanged from those of the previous day. The heart sounds were now of fair quality. The patient was given 1.6 mg. of lanatoside C (Cedilanid) during the day in divided doses. Later, on the same day, another observer thought there might be a precordial friction rub. The neurologic examination was entirely negative. That evening the patient was still disoriented and was grunting with each respiration. The pulse was 130, and the temperature was 102.6°F. It was noted that the area of decreased breath sounds at the left base had increased somewhat. He was given 0.2 mg. of digitoxin orally at this time and 0.2 gm. daily thereafter. An electrocardiogram revealed a sinus tachycardia at a rate of 200. The PR interval was 0.12 second, and the QRS interval 0.6 second, and the axis was 90°. The R waves were absent in Leads V_2, V_3 and V_4 and small in Leads 1 and aVL. The RS segment was small in Lead V_5 (Fig. 3). Bone-marrow aspiration from the left iliac crest was very cellular, but no specific diagnosis was warranted. A marrow culture yielded a growth of beta-hemolytic streptococci with good sensitivity to pencillin and other antibiotics. A blood culture yielded no growth.

On the fourth day it was noted that the patient continually held his hand over the lower left side of the chest, where he had severe pain. Thorough neurologic examination at this time was negative. He became cyanotic and incoherent and thrashed about in bed. The temperature was 104°F., the pulse 100, the respirations 60, and the blood pressure 100 systolic, 62 diastolic. Crysticillin, 300,000 units four times a day, and streptomycin, 1.0 gm. twice a day, had been started on the third day. Oxygen resulted in gradual disappearance of the cyanosis and in improvement of mental clarity. On the next day the left side of the chest was dull throughout, with markedly decreased breath sounds. The calves were not tender. The patient was given 200 mg. of Dicumarol; the oxygen was continued. The prothrombin time before the Dicumarol was 100 per cent of normal. A lumbar puncture revealed normal dynamics and normal spinal fluid. The next morning, the blood pressure was 90 sys-

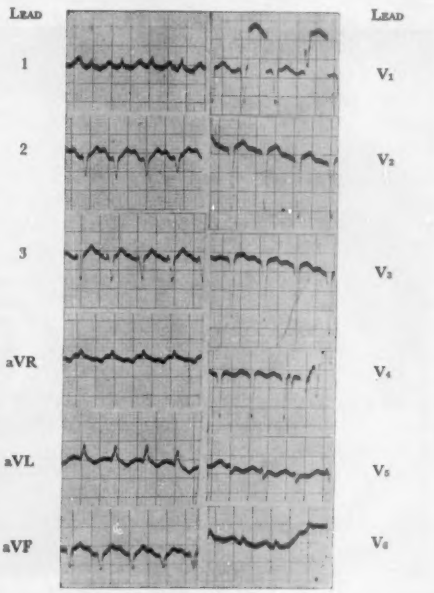

Figure 3.

tolic, 70 diastolic. The left side of the chest anteriorly had no tactile fremitus, no breath sounds, marked dullness and clearly transmitted voice sounds. The right side of the chest had expiratory musical rales basally. The hemoglobin was 10.3 gm. per 100 cc., and the white-cell count was 28,000, with 91 per cent neutrophils. The prothrombin time was 70 per cent of normal. An x-ray film of the chest revealed a massive left pleural effusion, with a shift of the trachea and heart to the right (Fig. 4). A thoracentesis through the eighth interspace in the left posterior axillary line yielded 800 cc. of grossly bloody fluid, which clotted. The fluid contained 27,000 white cells per cubic millimeter, with 90 per cent neutrophils, 6 per cent lymphocytes, 3 per cent monocytes and 1 per cent mesothelial cells, and had a hematocrit of 5 per cent. The cell block revealed no tumor cells. No acid-fast bacilli were seen on a smear of concentrated fluid. Culture of the bloody pleural fluid in thioglycolate yielded a growth of *Proteus vulgaris* overgrowing beta-hemolytic streptococci. Sensitivity studies on the beta-hemolytic streptococci subsequently revealed no inhibition by any of the antibiotics. A second dose of Dicumarol, 200 mg., was given, and the next day the prothrombin time was 38 per cent of normal. A single lateral film of the skull was normal. The Crysticillin was

increased to 600,000 units four times a day. There was marked limitation of motion of the right side of the chest, retraction of the left anterior rib margins and considerable abdominal distention. On the ninth day the prothrombin time was 25 per cent of normal. A repeat x-ray examination of the chest showed an increase in the amount of pleural fluid on the left; the right lung remained clear. A second thoracentesis yielded 250 cc. of grossly bloody fluid, which was obtained with difficulty from two taps. It was noted that multiple clots developed in this fluid on standing. After the thoracentesis the chest was tympanitic at the site of aspiration and was dull above and below this site. A cell block and cytologic smear of the pleural fluid yielded no evidence of cancer. The prothrombin time had now risen to 70 per cent of normal. The patient had received no Dicumarol for four days. Another electrocardiogram revealed that the rate was much reduced and the axis was much less to the left. Although the patient was no longer receiving oxygen the nail beds were only slightly cyanotic. On the tenth day, the prothrombin time was 60 per cent of normal; the hemoglobin was 9.4 gm. per 100 cc. The patient's general condition was unchanged during the next few days. The only medications were Crysticillin, 600,000 units four times a day, digitoxin 0.2 mg. and Demerol 75 mg. every four hours. He was given 500 cc. of packed red cells. Two weeks after admission thoracentesis was begun in the seventh interspace in the left posterior axillary line; after removal of 20 cc. of bloody fluid, the respirations became very shallow, and the pulse quite weak. The needle was immediately withdrawn, but the respirations ceased.

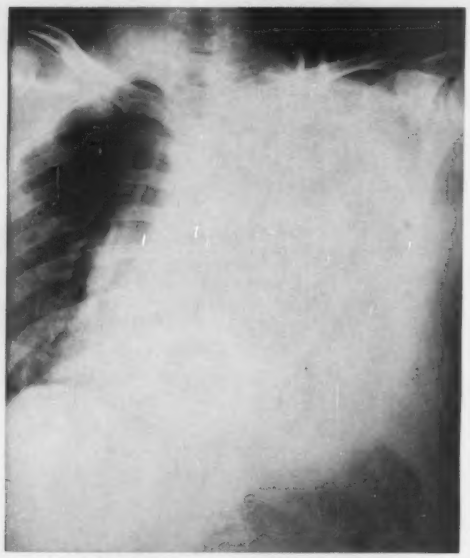

FIGURE 4. *Roentgenogram of the Chest (Four Weeks Later), Showing a Massive Left Pleural Effusion, with a Slight Shift of the Mediastinum to the Right.*

DIFFERENTIAL DIAGNOSIS

DR. MAURICE C. PINCOFFS*: We are now going to listen to a discussion, by three eminent clinicians, of the possible diagnoses in a case of unusual interest. Our first discussant will be Dr. Blumgart.

DR. HERRMAN L. BLUMGART†: I learned just a short time ago that my fellow Bostonian and friend, Dr. Castleman, had selected this case. I think you will agree that this case, therefore, clearly represents an instance of fratricide in this City of Brotherly Love.

The history begins with a reference to a tick bite. This tick bite and resultant lesion raise the question of Rocky Mountain spotted fever. The symptoms and clinical course are not indicative of this disease. There was no lymphadenopathy or rash. Neither do I believe that this patient had tularemia. The skin tests for tularemia should be positive by the end of the fourth day. The response to antibiotics would be striking in this disease. I do not believe the clinical course, with a high white-cell count and sepsis and with numerous negative blood cultures, all of which failed to reveal any organism whatsoever, is consistent with this diagnosis. The possibility of tularemia could have been dismissed if he had a skin test or complement-fixation test. I do not know whether they were done or not. Were they, Dr. Castleman?

DR. BENJAMIN CASTLEMAN: They were not done.

DR. BLUMGART: I do not believe the patient had tularemia. To go on, then, he had a clinical course of some fifty days from the time he came in until the time he died, and to that we may add the six weeks before he came into the hospital. As one goes over the entire history there is no evidence of relapsing fever. The possibility of periarteritis is suggested by several features, but I do not believe that this is the diagnosis. It would have to be localized to one area such as the lungs. There is no other evidence of periarteritis.

This man showed diverticulosis. As we review the entire history, two features are prominent. From the onset he had a dry, nonproductive cough, which persisted throughout the entire clinical course. The other impressive feature is the evidence of sepsis: high spiking fever and high-white-cell count, with neutrophils predominating. With diverticulosis of the bowel I considered the possibility that diverticulitis and peritonitis caused diaphragmatic irritation and gave rise to cough. Perforation through the diaphragm, leading to sepsis within the chest and to a septic course, would be consistent with certain

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†Physician-in-chief, Beth Israel Hospital; professor of medicine, Harvard Medical School.

aspects of this case. There are two features that militate against such a diagnosis. There was no evidence at any time on physical examination of tenderness in the left upper quadrant. The pain in the back might be consistent, but the abdominal examination was negative and the x-ray examination done in the midcourse of the disease revealed only diverticulosis. If there was a perforation into the chest, I should have expected that the pleural fluid would have been frank pus with organisms instead of a bloody fluid with 27,000 white cells.

This man had an old myocardial infarction. I believe he also had evidence of recent heart damage. In bizarre cases like this the possibility of a dissecting aneurysm should be considered. The pain of dissecting aneurysm is usually more marked than that in this case. There were no neurologic signs. If the dissection progressed anteriorly, I do not believe he would have had only an occasional episode of pain, with rupture into the pleural cavity.

The prominence of cough, the episodes of fever, the chest pain and the x-ray findings strongly suggest septic pulmonary infarction due to embolization. The syndrome of so-called right-sided bacterial endocarditis with insidious onset, prominent pulmonary disease, negative blood cultures until late in the clinical course, no clubbing of fingers or toes and spleen not enlarged is to be considered. There are two cultures in this case that are very important. The bone-marrow culture yielded beta-hemolytic streptococcus and a good sensitivity to penicillin and antibiotics. I do not believe we can treat that as a contaminant. We know the bloody pleural fluid also contained the beta-hemolytic streptococcus, which I do not think was a contaminant. Therefore, I would add to the diagnoses of old and recent myocardial infarction, pulmonary embolism and pulmonary infarction, the diagnosis of beta-hemolytic streptococcic bacteremia; we must look for the source of such an embolism. It is possible to have a silent focus without clinical evidence. Among such conditions, in a man with a previous anteroseptal infarct, is an infected mural thrombus on the septal wall of the right ventricle. It may have been a mural thrombus in the right atrium or a silent thrombophlebitis of the legs.

DR. PINCOFFS: Dr. Middleton, will you discuss your impression of this case?

DR. WILLIAM S. MIDDLETON*: The first part of the history, relating to the tick bite, is obviously a "fly in the ointment"; I think it is illusory. Conceivably, some infectious agent could have been introduced through this abrasion, particularly since the patient irritated the area. Such an infection could have occurred without lymphangitis, lymphadenopathy and thrombophlebitis. Indeed, this could conceivably have been the portal leading to the factors that have been so clearly covered by Dr. Blumgart. In clear focus is the occurrence of myocardial infarction with subsequent ventricular aneurysm. Does this circumstance fit into the total picture directly or indirectly?

Alpha-hemolytic streptococci were isolated from the throat on two occasions. While blood cultures were reported negative, a bone-marrow culture yielded a beta-hemolytic streptococcus. The constitutional reaction in fever, chills, leukocytosis and increased sedimentation rate calls attention to an infectious or septic background. The occasion of diarrhea after the use of antimicrobial agents, with a recurrence of fever, raises a natural question of a superimposed mycotic infection. When a hemothorax appeared in the left side of the chest, the number of white cells and the distribution of neutrophils in this pleural accumulation were singularly close to the respective figures in the circulating blood — an arresting point.

The conclusion of an infectious background for the ultimate picture seems inevitable. The bone-marrow culture and the culture of the pleural fluid yielded beta-hemolytic streptococci. Neither the portal of entry nor the focus of continuing infection was disclosed. No cardiac murmur was described. The heart had enlarged progressively. Recurring hemothorax, with pain in the left lower part of the chest, developed. The cerebral episode was probably embolic, a circumstance that could be explained on the same basis as a pulmonary infarction. Anticoagulant therapy was given in the presence of a hemothorax, after the cerebral accident.

The possibility of carcinoma of the pancreas has to be considered on the basis of the pain in the back. To most of you, this consideration may appear remote, but I have been deceived so frequently on such inconclusive grounds that I do not dismiss this diagnosis lightly. However, I do not believe that it is a consideration in this patient.

With the knowledge of the aneurysm of the left ventricle, on the basis of earlier myocardial infarction, can we dismiss the possibility of perforation of this area, with a resultant gradual hemothorax? It is my opinion that this patient suffered from a streptococcemia with a probable endocardial origin. As a further explanation a mural thrombus within the aneurysm of the left ventricle could well have been the potential source of the infection.

DR. PINCOFFS: Our third discussant will be Dr. Spink.

DR. WESLEY W. SPINK†: In trying to unravel this complicated clinical course, in which the illness extended over a long period, I have done what Dr. Chester Keefer taught me to do when confronted by a difficult clinical problem, and that is to chart out the course. There is little doubt that four years before this patient's death, at the age of forty-three, he had a myocardial infarction. He recovered from this illness after being kept in bed for seven weeks. During the succeeding three years he had repeated

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†Professor of medicine, University of Minnesota Medical School.

respiratory infections, including two bouts of pneumonia. He received antibiotic therapy intermittently. In this day of intensive study on gamma globulins and their relation to defense against infectious diseases, one must think of multiple myeloma and agammaglobulinemia. In both conditions the immune mechanism is deficient, and chronic and repeated infections occur. However, there is no satisfactory evidence to make a diagnosis of either condition. Three years after the myocardial infarction, and after repeated experience with infections and with antibiotics, Horton's cephalalgia developed. Was this in reality an expression of polyarteritis nodosa? Many organs seemed to be involved in this patient, and I see no way of ruling out this vascular disorder. Finally, we come to the terminal illness, in which a tick bite was implicated. This could suggest tularemia, but I see no further reason for considering this diagnosis.

This patient had sepsis, with chills and fever, with a leukocyte count ranging from 12,300 to 30,000, including a differential count of 98 per cent neutrophils. This does suggest mural thrombi on both the left and right ventricles, which were infected, thus producing a chronic endocarditis. This brings me to a discussion of the bacteriologic findings, which do not make sense. We read that a beta-hemolytic streptococcus, which was quite sensitive to penicillin, was cultured from the bone marrow. Then, later, we learn that beta-hemolytic streptococci were isolated from the pleural fluid. This culture was not sensitive to any of the antibiotics. If this was a Group A beta-hemolytic streptococcus exhibiting resistance to penicillin, it is the first time that such a resistant culture has been isolated from a patient. Group A hemolytic streptococci just do not manifest a high degree of resistance to penicillin. There is the remote possibility that this organism was a Group D streptococcus, or enterococcus, which rarely does produce a beta type of hemolysis. Group D streptococci are commonly associated with bacterial endocarditis.

I should interpret the massive bloody pleural effusion on the basis of multiple pulmonary infarcts and necrosis of the pulmonary parenchyma, which was secondary to the mural thrombi in the endocardium. In addition the debilitated condition of the patient and the intermittent use of antibiotics suggest the possibility of generalized moniliasis. I still think that periarteritis is a good possibility because of the albuminuria, coronary-artery disease and questionable involvement of the cerebral vessels. Is it possible that the needle inserted into the left pleural cavity just before he died suddenly entered a coronary artery?

My final diagnoses are old myocardial infarction with infected mural thrombi of the septum; pulmonary infarcts arising from the endocardial thrombi, and secondary pulmonary necrosis and left pleural effusion; cerebral emboli; and questionably periarteritis nodosa and terminal generalized moniliasis.

Dr. Pincoffs: My only comment on the last discussant's interesting remarks is to point out that some people prefer to hunt with a shotgun and others with a rifle.

Since we have a few minutes' leeway in time, and since there are many able clinicians assembled here in this audience, I am going to call on any one of them who has a diagnosis to offer to rise and give us the benefit of his impressions.

I take this lack of response to my invitation to indicate an excess of modesty on the part of the audience.

Clinical Diagnoses

Septicemia due to beta-hemolytic streptococcus.
Hemorrhage into left pleural cavity.
Myocardial infarction, old.

Dr. Herrman L. Blumgart's Diagnoses

Bacteremia, beta-hemolytic streptococcus.
Pulmonary embolization, with infarction, possibly from infected mural thrombus of right ventricle.
Myocardial infarction, old and recent.
Coronary arteriosclerosis.

Dr. William S. Middleton's Diagnoses

Streptococcemia, probably on basis of endocarditis.
Coronary thrombosis, with myocardial infarction, old.
Ventricular aneurysm, with infected mural thrombus.
Possible rupture of ventricular aneurysm, with hemothorax.
Pulmonary and cerebral embolism.

Dr. Wesley W. Spink's Diagnoses

Old myocardial infarction, with infected mural thrombi of septum.
Pulmonary infarcts from endocardial thrombi, with secondary necrosis and left pleural effusion.
Cerebral emboli.
?Periarteritis nodosa.
??Terminal generalized moniliasis.

Anatomical Diagnoses

Coronary-artery disease with mural thrombus, left ventricle, with secondary infection.
Myocardial rupture, left ventricle, through septic thrombus into left thorax.
Hemothorax, left (2500 cc.), with secondary infection.
(Septicemia, beta-hemolytic streptococcus.)
Myocardial infarction, old, anterior aspect of left ventricle and anterior septum, with aneurysm formation.

Coronary sclerosis, severe.
Cerebral infarcts, multiple, cerebral hemispheres and cerebellum.
Splenic infarct.
Pulmonary congestion and edema, right lower lobe, mild.
Bronchopneumonia, right lower lobe, mild.
Atelectasis, left lung, due to compression.
Hydrothorax, right (100 cc.).
Ascites, 200 cc.
Pericarditis, fibrous, old, obliterating pericardial cavity.
Arteriosclerosis, generalized, mild.

Pathological Discussion

Dr. Castleman: As is evident this patient was studied very carefully over a number of weeks, and I might say that the men who were taking care of him were really baffled.

At post-mortem examination the first thing that was obvious was the large amount of hemorrhagic fluid in the left pleural cavity — 2500 cc.; it not only was hemorrhagic but also contained large amounts of fibrin so that it was obviously an infected hemothorax. In the apex of the left ventricle of the heart was an aneurysm resulting from the old myocardial infarction, on which was a red, granular, soft mural thrombus. The pericardial cavity was obliterated. This photograph (Fig. 5) was taken after the parietal pericardium was separated to show that there was an actual perforation of the ventricle in the region of the mural thrombus. The perforation, because of the obliterated pericardial sac, extended directly through into the pleural cavity, and here is where we found the 2500 cc. of hemorrhagic pleural fluid. Microscopical examination of the ruptured ventricular wall showed fairly well the infective nature of the mural thrombus with fibrin and polymorphonuclear leukocytic infiltration of not only the mural thrombus but parts of the underlying aneurysmal wall (Fig. 6). We looked very carefully for organisms and made all sorts of bacterial stains, but were unable to find any that we could be sure were organisms. Evidence of embolization was found in many of the glomerular tufts of the kidney. There were many infarcts in the brain and a large one in the spleen.

Figure 5. *Cardiac Aneurysm at the Apex of the Left Ventricle, with Superimposed Mural Thrombus* (A). *White paper extends from perforated heart (left) into obliterated pericardial cavity — separated for photograph —* (B), *and finally into left pleural space* (C).

Figure 6. *Photomicrograph of the Heart, Showing a Mural Thrombus on the Fibrotic and Thinned-out Aneurysmal Portion of the Myocardium.* *Note the inflammation, necrosis and fibrinous exudation involving the inner half of the myocardium.*

In attempting to correlate the clinical picture with the anatomic findings, I believe that before the third admission to the hospital the patient had an upper respiratory infection, was treated with Crysticillin, did well but was not completely cured.

Then, when he came into the hospital, the organisms had apparently already settled in the mural thrombus on the old cardiac aneurysm. This would account for the febrile hospital course. The pain in the left anterior part of the chest during the fourth and last admission was probably related to the rupturing process. I do not think he had a massive rupture and sudden death. There were probably subsequent bleedings into the left pleural space during the remaining days of life, but the pressure of the accumulated pleural blood prevented overt exsanguination. It is comparable to the slow perforation in some dissecting aortic aneurysms, with the gradually increasing accumulation of blood in the pericardial or pleural cavities.

Myocardial rupture caused by a septic process is extremely rare. Brown and Evans[1] described a case of myocardial rupture through a calcified myocardial infarct. Their patient had a bacteremia arising from a perinephritic abscess and the organisms localized in the myocardial aneurysm leading to the rupture. It is interesting that, in the recent series of 108 cardiac aneurysms reported by Schickter, Hellerstein and Katz,[2] not a single case was associated with superimposed sepsis. Although the case under discussion today is the first septic mural thrombus that I have seen in the heart, recently we have had two in the abdominal aorta: in 1[3] a mural thrombus in an arteriosclerotic abdominal aneurysm was infected with streptococci, apparently from an erysipeloid infection of the skin; the other was a mycotic aneurysm caused by salmonella[4]; both had perforated and led to death. I do not know whether the antibiotic treatment that we are now using may be the reason why we are now seeing more settling of virulent organisms in mural thrombi in the same way that staphylococcal enteritis is seen after the use of antibiotics. Dr. Dammin,[5] of the Peter Bent Brigham Hospital, tells me that he has seen 3 cases of sepsis that developed in mural thrombi.

DR. PINCOFFS: Were there any infarcts in the lungs?

DR. CASTLEMAN: The only involvement in the lungs was some pneumonia in the right lower lobe. The left lower lobe was collapsed, with no evidence that the collapse was any more than a pressure atelectasis. There were no pulmonary infarcts or infection in the lungs. I think the discussers are to be congratulated for considering infected mural thrombus, which was not considered when the patient was on the ward.

DR. PINCOFFS: Thank you very much, Dr. Castleman, for your interesting presentation of these pathological findings. I have seen a case that presented an interesting variation of essentially the same process that has been discussed here. In this case an aneurysm of the ventricular wall perforated the wall but was contained by a thick adherent parietal pericardium. This pericardium had been dissected off the exterior of the ventricle for a distance of some centimeters about the point of perforation; thus, the left ventricular cavity communicated through the perforation with a second pocket of blood under the pericardium. In this patient, during convalescence from the acute myocardial infarction, a considerable effusion in the left pleural cavity appeared. After this clear fluid had been removed by thoracentesis the presence of what was taken to be a usual ventricular aneurysm was easily made out by roentgenography.

DR. CASTLEMAN: I should like to ask Dr. Spink to comment on whether he has noted a greater incidence of sepsis in mural thrombi of aneurysmal walls.

DR. SPINK: I cannot answer your question because I have not seen enough cases of mural thrombi involving aneurysmal walls that have been studied bacteriologically. I am still perplexed by the bacteriologic reports on this patient, and can only conclude that there was some doubt about the precise type of hemolytic streptococcus isolated from the patient. If he had a chronic infection due to Group A hemolytic streptococci, he lived an unusually long time.

DR. CASTLEMAN: There is no evidence of infection at this time. The changes in the myocardium could all be explained by sepsis, and the necrosis in the myocardial fibers was due to sepsis and not to infarction.

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ANTIBIOTICS, STAPHYLOCOCCI AND ENTEROCOLITIS

MORE than two years have elapsed since the subject of staphylococcal enteritis and pseudomembranous enterocolitis and their relation to antibiotic administration was reviewed and discussed in these columns.[1] In that discussion a distinction was made between staphylococcal diarrhea, or enteritis, which was considered to be a specific complication of antibiotic therapy associated with replacement of the bowel flora by antibiotic-resistant staphylococci, and pseudomembranous enterocolitis, which was considered to be a distinct entity, chiefly a complication of surgery of the bowel or associated with other disease of the bowel, in which the antibiotic therapy and the staphylococcus were incidental complicating factors. Numerous reports of additional cases and discussions of this subject have appeared since that time. Representative reports from among those that have appeared in the past two years and some more recent studies bearing on this subject seem worthy of summary and further comment.

Terplan et al.[2] recorded 8 cases of fulminating gastroenteritis in which major surgical operations were performed, accompanied by the administration of broad-spectrum antibiotics (including a combination of penicillin and streptomycin) and in which death occurred three to eleven days postoperatively. Large masses of staphylococci were seen within the desquamated or loosely adherent pseudomembranous exudate covering the mucosal coat, particularly in the small intestine. The recent inflammation was, in general, restricted to the mucosa and submucosa. Staphylococci were cultured from the intestinal tract or the lungs, or both, in 5 cases. The authors interpreted the clinical course and pathological findings, particularly the bacterial stains of the tissue sections of the gastrointestinal tract and the degenerative changes in the adrenal glands and kidneys, as indicating a severe toxic state from staphylococcal infection, but not a septicemic process.

Williams and Pullan[3] described 10 cases, observed during the previous five years, in which severe diarrhea associated with circulatory collapse occurred two or three days after operations on the stomach for various conditions. Five of the patients died, and each showed necrosis of the mucosa of the bowel at autopsy. There was no peritonitis, and the anastomoses appeared healthy. There was some sloughed membrane of the mucosa on the small bowel, often patchy, usually starting distal to the anastomosis and not involving it. The submucosa was relatively normal. The authors considered the condition analogous to partial-thickness skin loss and equally favorable for recovery.

Bacteriologic studies were made of the stools in vivo or of the bowel contents in 8 patients. In 2 there were no pathogens; miscellaneous organisms were

obtained in 3, and staphylococci were found in only 3, including 2 who received chlortetracycline postoperatively. Staphylococci of the same phage group were observed in the normal stools of several patients on the same wards. Swabs of the stomach and small bowel, and of the nose in 1 case, were cultured at the time of operation; none of them yielded staphylococci although this was later found in the stool during the acute episode. There was therefore no organism common to all the cases, and staphylococci of the same phage type were frequent in unaffected cases.

Some of the patients had received antimicrobials before and after operation, and most of them had not; in most cases sulfamerazine was used preoperatively and penicillin or streptomycin, or both, postoperatively. Chlortetracycline was given intravenously after the condition was recognized in 3 cases and was considered of doubtful value since it did not affect the fundamental difficulty, which was fluid loss. When the condition was recognized and adequate fluid replacement promptly instituted the patients improved immediately; rapid infusion of large quantities of fluid were often required. In the patients who recovered, the diarrhea stopped within a week, and there were no late complications.

Williams and Pullan[3] concluded that the etiology of their cases remained obscure. Nutritional factors played no part, operative difficulties were encountered in only 2 cases, and there was no gross fall in blood pressure. Operative trauma seemed to be excluded by the good gastric, duodenal and jejunal mucosa near the stoma, and one of the operations was even done without clamps. The authors stated: "Although the etiology is unknown, the clinical picture is sufficiently characteristic to provide the diagnosis and to indicate treatment which, if adequate and prompt, will insure a happy outcome in a desperate condition."

Another interesting group of cases was reported and discussed by Prohaska, Govostis and Taubenhaus,[4] who described 3 patients in whom pseudomembranous enterocolitis developed after surgery of the colon. Each had received phthalylsulfathiazole and oxytetracycline preoperatively. After surgery they became gravely ill; in 2 reoperation was performed, and a diagnosis of pseudomembranous enterocolitis was definitely established. All 3 recovered rapidly a few days after treatment with ACTH. Four other patients who received intensive supportive therapy without ACTH died, and the diagnosis of pseudomembranous enterocolitis was made at autopsy; only 1 of these patients had received any preoperative chemotherapy (phthalylsulfathiazole and oxytetracycline).

These authors therefore question the assumption that pseudomembranous enterocolitis is due to the preoperative use of antibiotics. They also believe that shock is not a major cause of the disease, but they offer speculations based on the favorable response of their 3 patients to ACTH. They do not consider it to be an infection, which the ACTH would have aggravated. (This reasoning, however, is not necessarily valid.) Nor do they consider the enterocolitis to be of endocrine origin, since endocrine dysfunction is not associated with pseudomembranous lesions in the intestinal tract and the beneficial effects of ACTH could be ascribed only to the pharmacologic effects of the steroids stimulated by the ACTH. No answer was offered, and the true cause was considered to be still unknown.

Pettet et al.,[5] in one of many papers on this subject emanating from the Mayo Clinic, reviewed the clinical, laboratory and autopsy records of that clinic from 1925 through 1952. They found 94 patients who had died postoperatively with pseudomembranous inflammation of the gastrointestinal tract. Nonsurgical patients were excluded, for these cases had already been reported by Kleckner, Bargen and Baggenstoss[6] (this article was discussed previously[1]). The authors reiterated that the condition had not increased in recent years; there were 45 cases in the fourteen years before chemotherapy and 49 in the fourteen years since 1938. However, whereas the correct diagnosis was not made clinically before 1948, it was correctly diagnosed ante mortem in 14 of 26 cases after then. Almost all the patients had had operations on the gastrointestinal tract. There was no one etiologic factor, but carcinoma of the colon was frequent and the associated septic processes and some degree of obstruction seemed significant.

The findings of numerous staphylococci in the recent cases suggested that a change in the normal balance of the intestinal flora may be important in producing the lesion. However, this balance may be upset by intestinal obstruction in some cases, by therapy in others and by factors as yet unknown in still others. In the discussion of this paper, Baggenstoss pointed out that in the preantibiotic era, 75 per cent of the cases of pseudomembranous enterocolitis were complicated by generalized peritonitis, as compared with 47 per cent in recent cases. Peritonitis may cause toxic lesions and adynamic ileus or intestinal obstruction; the obstruction by itself may cause changes in the flora even without the use of antimicrobials.

In the earlier comment[1] the possibility was considered that an enterotoxin produced by the staphylococcus might be involved in the pathologic process and particularly in the symptoms, and the condition was empirically ascribed to such an enterotoxin by some writers[7] but no enterotoxin had actually been demonstrated. Recently, Surgalla and Dack[8] were able to demonstrate enterotoxin production by 30 of 32 strains of staphylococci obtained from patients with enteritis after antibiotic therapy. This finding

supports the hypothesis that an enterotoxin is produced in vivo by antibiotic-resistant, food-poisoning strains of staphylococci and may account for the toxemia in the cases under discussion.

The situation is different in ordinary staphylococcal food poisoning, in which the enterotoxin is produced in food outside the body and there is no further enterotoxin production in vivo. Moreover, in food poisoning, some of the toxin that has not been absorbed is probably eliminated in the vomitus and diarrhea, and further multiplication of the staphylococcus and enterotoxin production is inhibited by the normal bowel flora. In the staphylococcal enteritis that follows antibiotic therapy, on the other hand, enterotoxin may continue to be produced as long as the normal bowel flora is suppressed.

Surgalla and Dack explain the relatively infrequent cases of staphylococcal enteritis during antibiotic therapy by the common occurrence of antibiotic-resistant coliform and other intestinal bacteria or possibly by predominantly nonenterotoxigenic staphylococci. The patients in whom staphylococcal enteritis develops may be only those whose normal intestinal flora is sensitive to the antibiotics used while a resistant strain of enterotoxigenic staphylococcus is present.

These findings of Surgalla and Dack, and many of the clinical reports not mentioned here, stress the role of antibiotic therapy and the predominance of staphylococci in the intestine as the major or only factor in the cases of staphylococcal enteritis, without differentiating the cases of pseudomembranous enterocolitis, which, according to some of the reports mentioned here and previously,[1] are associated with neither antibiotic therapy nor staphylococci. This appears also to be the general view as expressed in a recent editorial,[9] which concludes with the statement, "The causative factor appears to be the emergence of antibiotic-resistant micrococci and their effect on the intestinal flora of the post-operative patient."

Some light on the possible mechanism of the production of pseudomembranous enterocolitis comes from experiments in dogs, reported recently by McKay et al.[10] They produced pseudomembranous enterocolitis in dogs by the administration of incompatible blood into the aorta, with concomitant surgical trauma consisting of laparotomy, repeated renal biopsies and left-sided nephrectomy. The intestinal lesions were caused by thrombosis of capillaries of the intestinal mucosa, resulting from intravascular clotting and "compensated" shock with arteriolar constriction and pooling or stasis of blood in the dilated splanchnic capillaries. The clinical syndrome and pathological lesions in the dogs were similar to those of pseudomembranous enterocolitis in man.

These authors suggested that the pathogenesis of the lesion in man depends on the same two factors — namely, intravascular clotting and stasis of blood in the capillaries of the intestinal mucosa. Obviously, if similar factors are involved in cases in human beings, the search for the cause, prevention and cure of this condition lies in an entirely different direction from that suggested by bacteriologic features, which may nevertheless be the primary factors in the cases of staphylococcal enteritis that complicate antibiotic therapy. Obviously, the bacteriologic factors must be considered and dealt with in either condition, but prevention and management of pseudomembranous enterocolitis require an attack based on the fundamental mechanism involved in its production.

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JOSEPH H. PRATT, PIONEER

On June 20 the New England Medical Center, in collaboration with the Massachusetts Council of Churches, held a full-day conference commemorating Dr. Joseph Hersey Pratt's fifty years of pioneering in group therapy. He had begun his work on July 1, 1905, with a group of 8 patients with pulmonary tuberculosis living in crowded districts of Greater Boston, for whom no place could be found in the sanatoriums then available.

Though prolonged outdoor rest for his patients on roofs and improvised porches or in tents in the backyards of their homes, visited by a friendly trained worker and supported financially by the Emanuel Church, was one of the features of his method, an equally important measure was the weekly meeting of the group at the Massachusetts General Hospital, where the members were weighed, their temperature and pulse taken and their personal, detailed record books reviewed. The greatest gains in weight were posted conspicuously, and the member who remained at rest longest during the week had his record book exhibited. Thus, a spirit

of healthy competition was stimulated. All members were seen in turn individually; their questions were answered, and advice given. Dr. Pratt also gave the group as a whole a short talk with some advice and encouragement. His results in time equaled and even surpassed those of the State sanatoriums, and similar classes were organized both in this country and abroad.

Dr. Richard C. Cabot, founder of modern medical social service, was one of the first to recognize the value of the Pratt "class method," and a year after the formation of the first class, he predicted that it would soon be applied to every common chronic disease, as it eventually was. In 1908 William R. P. Emerson organized at the Boston Dispensary his first class for undernourished children. Soon, also, group treatment of diabetic and of cardiac patients was begun at the Peter Bent Brigham Hospital, and in the years to follow, the method was applied to practically all chronic diseases with great success all over the world.

Early in his career Dr. Pratt had acquired a second great interest through becoming acquainted with Dejerine's *The Psychoneuroses and Their Treatment by Psychotherapy.* In 1929 he was appointed physician-in-chief of the Boston Dispensary. There, with the understanding interest and financial support of William Bingham and with the co-operation of men and women whom he had attracted from all parts of the country and from Europe, he established in time one of the best diagnostic and research and rural medical training centers in the country. In 1930 he began to treat his patients by the method of Dejerine at the Dispensary, where, in a survey of 2000 consecutive admissions to the medical clinic, no less than 36 per cent were found to be suffering with psychoneurosis. Here, as in his "tuberculosis class," he employed group therapy as adapted to psychoneurosis in weekly meetings and with equally striking results. Again, his pioneering led to the wide adoption and progressive application of group psychotherapy all over the world to all types of neurosis, to psychosis and to the tensions in social groups, in the armed forces and even in the prisons, touching the fields of physician, psychiatrist, psychologist, social-service worker and chaplain.

For over half a century Dr. Pratt has had a dynamic influence in Boston. A New Englander, trained at Yale and at Johns Hopkins, he brought here the traditions and culture of Chittenden, Welch and Osler, as manifested in his work as clinician, investigator and teacher. Blazing new trails in the alleviation of human ills, he takes rank in the gloriously long line of his fellow townsmen who helped, in large measure, to raise medicine in America from very lowly beginnings to its present high level. May we enjoy his cheering presence for many years!

OPERATION EVACUATION

A RELUCTANT realization of the fact that there is no adequate protection from a thermonuclear blast has necessitated an entirely new concept of civil defense, so-called, no less disturbing than the old one of hurrying to the least ineffective available shelter. For there is now no hiding from the effects of a sundered atom.

Flight alone has become the order of the day if there is sufficient time for flight in the event of an attack, and with the changed order comes a new set of rules to follow. Certain highways are no longer reserved for the influx of defensive personnel and material; when Rome is threatened all roads lead away from Rome, the city is left to those too calloused to flee or incapable of it, and the ways of egress become choked with humanity, possibly in panic — for nothing breeds panic so much as flight.

Elsewhere in this issue of the *Journal,* in the Civil Defense section, Maher brings up the problem of medical care of the sick and wounded, who might be counted in the hundreds of thousands, if such an attack on any of the cities of Massachusetts took place without ample warning having been received. Work is going forward on these problems, and surveys of resources of personnel and plans for supplies and equipment have been and are being made.

Hospitals may be affected in two ways — by being involved in the disaster or by being called on to receive casualties. Hospitals in the target area are liabilities in that their population must be evacuated to other parts; those outside the area must expand their facilities to receive casualties and the patients who may have been successfully evacuated from the hospitals involved. In order to increase these facilities buildings throughout the Commonwealth have been assessed for conversion to hospital use, and some 1600 have been selected. To render them effective, equipment for 200-bed improvised hospital units is being purchased. So far only 7 such units are available; they represent a step in the right direction, but the task and the cost of complete preparation are too stupendous to be more than contemplated. The specifications of a knocked-down mobile hospital, which can be transported in a single van, have been carefully worked out; they include supplies for forty-eight hours of continuous operation.

Such preparation in terms of physical equipment and of trained personnel makes sense, up to a reasonable point, even for times when the world seems dedicated to peace. It is an orderly preparation for such natural catastrophes as those caused by fire, wind and flood, from which monotheistic man asks his God to deliver him, not always with completely satisfactory results.

An actual comprehension of the total or near-total

evacuation of a metropolitan area about to be totally eradicated leaves more to the imagination than the imagination can cope with. Not all the people who take to the road will be law-abiding citizens; one can hardly visualize the possibility of such an exodus sweeping over the countryside like a swarm of locusts, denuding it on the way, unless adequate military protection should become unexpectedly available to ride herd on the refugees. Had the catastrophe already occurred the problem would, in a way, be simplified — there would be fewer evacuees.

There are many details of such an operation on which no one seems as yet to have been enlightened. The best defense at the moment would appear to lie in a diplomacy so astute and realistic that the occasion for an evacuation could never arise.

EIGHTH WORLD HEALTH ASSEMBLY

THE eighth Assembly of the World Health Organization, in the matter of administrative functions, elected six countries to its executive board at the recent meeting in Mexico City, which ended on May 31. The countries thus chosen to delegate representatives to the 18-member board for a three-year term were Argentina, Pakistan, the Republic of the Philippines, Ecuador, Portugal and Finland. At the same meeting the Sudan was admitted as an associate member of the Organization, bringing the total to 85.

A budget of $10,203,084 for 1956 to finance over 300 major international health programs throughout the world was adopted. The three major projects to be featured in the over-all plans for the year are continued efforts toward the eradication of malaria, the public-health aspects of the use of atomic energy and expansion of the international poliomyelitis program. An earnest inquiry into the hazards of radioactive fallout and the problem of radioactive-waste disposal was considered to be an urgent necessity of the day and one to be vigorously pressed by all responsible and qualified agencies.

The Assembly, which was presided over by Dr. Ignacio Morones Prieto, secretary of Health and Welfare of Mexico, was the first to be held in the Western hemisphere and the second to meet outside WHO headquarters in Geneva. It was attended by delegates of 76 of its 84 member states, representatives of the United Nations and specialized agencies and observers for 25 intergovernmental and nongovernmental agencies concerned with public-health activities.

Abortive Treatment of Coryza. — *M. Yvonneau states that during several years he has always succeeded in arresting idopathic coryza within twenty-four hours, by the simple expedient of occluding the nostrils.*

Boston M. & S. J., *August 9, 1855*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

REYNOLDS — John Andrew Reynolds, M.D., of Springfield, Massachusetts, died on June 28. He was in his sixty-third year.

Dr. Reynolds received his degree from the Long Island College of Medicine in 1922. He was a fellow of the American Medical Association. He was cardiologist and metabolist at Wesson Memorial Hospital.

He is survived by his widow.

CIVIL DEFENSE AGENCY

MEDICAL PLANNING FOR CARE OF MASS CASUALTIES IN DISASTER

In long-term planning to establish emergency medical care for great numbers of casualties in a disaster it is necessary to analyze existing resources of medical personnel, hospital facilities, medical equipment and supplies within the Commonwealth. The optimum benefit will be derived from these resources in combating any disaster by comprehensive and detailed planning beforehand.

In an enemy attack without warning with thermonuclear weapons the major cities of Massachusetts would have several hundred thousands of surviving casualties needing immediate hospitalization. Therefore, the great destructive power of modern thermonuclear weapons makes it imperative, if time permits, to have planned evacuation carried out from specified target zones of major cities. Such factors of medical significance as radioactive fallout and available shelter therefrom will determine whether or not evacuation will be successful. Evacuation of population from major cities without due consideration of these hazards would inevitably cause great numbers of deaths. Other factors, which are nonmedical but on which medical planning to be successful will ultimately depend, will be the capacity of evacuation routes from major cities and the capacity of Civil Defense authorities in planning to mobilize all facilities for accomplishing evacuation within the shortest time and under the most adverse circumstances. Of no less importance is long-range planning for dispersal of population and industry and for highway construction.

In Massachusetts state-wide surveys have been undertaken of available resources of 30 different classes of hospital personnel that would be needed to staff emergency hospital installations in the event of

disaster. The location of such personnel by city and town will be of much assistance to hospitals in the event of disaster. Manuals that outline training programs have been developed for equipping technical personnel with the various skills.

The total liabilities of the Commonwealth in the event of sudden disaster are determined by studies of expected casualty loads in critical target areas. These studies include not only the total casualty load expected from various types of thermonuclear devices but also a total of the types of injuries sustained among the surviving casualties. Resources of medical facilities, supplies and equipment and how they may best be utilized, whether or not evacuation of the general population from critical target areas is achieved, will have to be considered. To meet this liability 300 mobile casualty stations have already been dispersed in more than 100 cities and towns of the Commonwealth. Essential medical supplies are also dispersed at more than 30 other locations, outside critical target areas, and inventories have been taken of other sources of available medical supplies that would be urgently needed by physicians.

Successful mobilization of hospitals to combat any sudden disaster can only be accomplished by detailed preparation. Hospitals are now developing comprehensive disaster planning for their personnel and facilities. Two distinct phases may be considered in this planning:

Plans to be put into operation if the hospital is directly involved in the disaster (that is, located within the disaster area).

Plans to be put into operation if the hospital is not involved in the disaster but has the function of receiving and caring for large numbers of casualties.

The first plan may involve several eventualities:

The warning of an impending attack does not provide sufficient time for evacuation; therefore, patients and personnel must seek whatever protection is available within the hospital.

The warning of an impending attack does provide sufficient time for evacuation of patients and personnel.

Parts of the hospital are damaged, or personnel are unable to function.

The second plan includes the following eventualities:

General hospitals will be requested to receive and care for casualties up to several times their normal bed capacity.

Hospitals for nervous and mental disorders will receive and care for casualties in accordance with a special plan developed for this type of institution.

Hospitals for communicable disease will expand to receive patients with communicable disease or victims of biologic warfare.

Efficiency of disaster organization can only be obtained by periodic maneuvers and drills involving all hospital personnel.

Many hospitals in the Commonwealth are located within critical target areas and would probably be rendered inoperable in the event of a large-scale disaster such as an enemy attack. It is therefore imperative to exclude from long-term planning the available bed space in all hospitals located in critical target areas. A step toward the solution of the ensuing problem is the development of an improvised hospital system that makes maximum use of existing facilities; this system will ultimately be composed of 200-bed units, which will provide early and mobile hospital facilities for casualties in the vicinity of disaster areas.

In assessing the magnitude of the problem that confronts this emergency hospital system, one should consider existing designated critical target areas in the Commonwealth and the estimated number of surviving casualties to be expected therefrom. The total number of casualties needing immediate hospitalization and the types of casualty most likely to be encountered may be calculated from a knowledge of the type of bomb used and the point of detonation.

To meet the direct needs of hospitalization in a large-scale disaster a survey has been made of all public buildings throughout the Commonwealth capable of being converted into hospitals. This survey takes into consideration all schools, auditoriums, gymnasiums, halls and churches, together with their facilities, that would be of assistance for conversion into an improvised hospital system. Approximately 1600 public buildings were chosen throughout the Commonwealth for this system.

Hospital bed space available in the Commonwealth is shown in Table 1.

TABLE 1. *Existing and Potential Hospital Bed Space in Massachusetts.*

TYPE OF BED CAPACITY	NO. OF BEDS
Existing	64,512
Expanded	75,928
Improvised	216,262
Total potential	356,702

Seven 200-bed improvised hospital units have been purchased by Massachusetts. One 200-bed improvised hospital unit can be installed in any suitable large public building, and a space of approximately 15,000 square feet is required for each unit. It may be installed in any suitable location for immediate use by 30 trained personnel and auxiliaries in approximately four hours. This hospital will be mobile and will thus greatly facilitate existing hospital and medical planning based on the fundamental principle of dispersal. The particulars of the hospital unit are designed on the principle of the 60-bed mobile army surgical hospital, which effectively provided surgical

care for seriously wounded casualties at the front lines of combat in the Korean conflict.

The improvised hospital is composed of 288 different types of equipment, including 5 folding operating tables and a portable field x-ray unit, surgical equipment and drugs. It weighs approximately 14 tons, occupies approximately 2000 cubic feet of storage space and is composed of 450 separate packages, which can be transported in a single van. Sufficient expendable medical supplies are stored with this unit to enable continuous operations for forty-eight hours during a disaster. The total cost of a 200-bed improvised hospital unit is $26,500. When installed in a public building such as a school or gymnasium, this hospital would include the following items: triage room, shock-treatment ward, 3 operating rooms, sterilizing room, central supply room, pharmacy, laboratory and x-ray plant capable of producing sixty-second x-ray films with its own portable generator and transformer.

To ascertain the optimum distribution for 200-bed hospitals of this kind, studies are being made of population density and the location of critical target areas. In this way cardinal principles of mobility and dispersal in planning for medical civil defense will be adhered to so that the greatest possible utility will be derived from this unit. The 200-bed hospital unit is the result of a prolonged survey conducted by hospital and medical personnel of the armed forces and Civil Defense authorities at Hiroshima and Nagasaki. It is hoped that in this way a system can be developed for establishing emergency hospitalization for casualties in any large-scale disaster.

The 200-bed improvised emergency hospital unit can be effectively utilized in a large-scale natural disaster such as a tornado or hurricane to supplement any existing hospital needs. A manual of procedures that will be developed in co-operation with the Massachusetts Medical Society will outline the staff organization and operation of the unit. This manual will be of invaluable assistance to physicians in the organization of triage and operating teams, which are extremely important in establishing an emergency hospital system. Although it is not within the scope of this manual to consider the principles of triage and emergency surgical procedures as applied to large-scale atomic disasters, they are of such importance as to warrant separate consideration.

THOMAS F. MAHER, M.D., D.P.H.
Executive Medical Officer

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CORRESPONDENCE

WEIGHT-REDUCING DIETS

To the Editor: The relative efficiency of high-fat and high-carbohydrate diets in weight reduction of the obese has been studied extensively, and most of the investigators have found high-fat diets superior. The same observation has been made in the genetic obesity of mice. Dr. Werner's studies, however, as reported in his article, "Comparison between Weight Reduction on a High-Calorie, High-Fat Diet and on an Isocaloric Regimen High in Carbohydrate," in the April 21 issue of the *Journal*, led him to conclude that there was no difference between the two types of diet. Dr. Werner's findings do not seem to me to lead unequivocally to the conclusion he has drawn. His chief positive evidence is derived from the case of a sixteen-year-old boy, E.W., weighing 380 pounds (174 kg.). This seems to be one of the rarer forms of obesity and not representative of the majority of cases. Another case, D.W., was reported as similar, but the findings were not given.

Of the other 4 cases in the series 1 was complicated by diarrhea, and 2 by menstruation, and the weight losses were attributed to shifts in the sodium and water balance. Of these cases the sodium balance in only 1 (G.W.) was shown; the change to the high-fat diet was followed by a slight loss of sodium for three days, attributed to menstruation at this time. However, weight loss continued during the period of positive sodium balance that followed, in spite of the fact that the sodium intake on the high-fat diet was higher than it had been on the high-carbohydrate diet. It seems difficult to avoid the conclusion that increased oxidation of body fat must have been responsible for some of the weight loss on the high-fat diet. (According to the balance chart of this case, Figure 5, the change in diet took place on the twenty-fourth day, rather than on the twentieth day as the arrow in Figure 4 suggests.)

In his discussion Dr. Werner called attention to the ability of large groups of people to grow and to develop on a high-fat diet, presenting this as evidence that such a diet could not be expected to promote weight loss in the obese. It seems that he has failed to take into account a reasonable body of evidence that has accumulated that the obese are metabolically different from those of normal weight. Kekwick and Pawan, as stated in a personal communication from Pawan, recently found a marked increase in the metabolism of the obese during the first few hours after a high-fat meal. The whole question of fat versus carbohydrate in the diet of the obese is a very challenging one, and it does not seem that it can be dismissed on the basis of the data that Dr. Werner has presented.

A. W. PENNINGTON, M.D.
Wilmington, Delaware

Dr. Pennington's letter was submitted to Dr. Werner, who offers the following reply:

To the Editor: Dr. Pennington has raised several points in his letter concerning our recent study. Owing to stringencies of space only a limited number of graphs could be presented in the article. All graphs, however, had been submitted for publication, and the data are available.

It should be reiterated that patients E.W. and D.W., commented upon by Dr. Pennington, showed virtually identical weight losses and balance data with the two forms of diet, except as mentioned in our paper. Patient D.W. is an active and healthy, although obese, male nurse working in the hospital. Patient E.W. is a large Negro boy with many emotional problems. There is no ostensible reason on clinical grounds to distinguish him from the other patients of the study except for his greater weight.

In patient G.W., the initial diet period ended as indicated in the published graphs, and not at twenty-four days as suggested by Dr. Pennington. Again, the balance data of the other patient that were not published are available for inspection and are very similar.

The essential question posed by Dr. Pennington's various publications and investigated by us was not whether obese patients on a high-fat diet can or cannot lose weight but whether they can eat unlimited amounts of fat and still

lose weight, or whether they can lose weight better with high-fat diets than with isocaloric high-carbohydrate diets. Our experience indicates, first of all, that not all patients lose significantly while eating a high-fat diet and, secondly, that patients who do lose, lose the same whether the diet is rich in carbohydrate or in fat.

SIDNEY C. WERNER, M.D.

New York City

REVOCATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held July 12, 1955, it was voted to revoke the registration to practice medicine of Dr. Italia D' Argenis (Granata), 108 Shrewsbury Street, Worcester, Massachusetts.

Robert C. Cochrane, M.D.
Secretary

State House
Boston

NOTICES

ANNOUNCEMENT

Dr. Leo B. Burgin announces the removal of his office to 151 Kent Street, Brookline 46, Massachusetts.

Dr. Angela C. Duffy announces the opening of an office for the practice of pediatrics at 6 Hubbard Street, Concord, Massachusetts.

Dr. Raymond Gelfman announces the removal of his office for the practice of internal medicine and cardiology, to the new Medical Center Building, 130 Maple Street, Springfield, Massachusetts.

Dr. Melvin H. Levin announces the opening of his office for the practice of radiology at 894 Commonwealth Avenue, Newton Centre 59, Massachusetts.

GREATER BOSTON MEDICAL SOCIETY

The program of the Greater Boston Medical Society for the coming year is as follows:

October 19, 1955	Smoker.
December 14, 1955	Scientific meeting.
February 15, 1956	Dinner — combined.
March 28, 1956	Maimonides awards.
April 18, 1956	Dance.

ESSEX NORTH DISTRICT MEDICAL SOCIETY

The fall meeting of the Essex North District Medical Society will be held at the Haverhill Country Club, Haverhill, Massachusetts, September 21, 1955. The dinner will be at 6:45 p.m.

AMERICAN MEDICAL ASSOCIATION

A program of medical motion pictures is being planned as part of the program of the Clinical Session of the American Medical Association meeting in Boston, November 28—December 2, 1955. Those interested in having their productions presented during the meeting may obtain information from Dr. Norman Lenson, Division Chairman, Medical Motion Pictures, 1093 Beacon Street, Brookline 46, Massachusetts.

The deadline for the program has been established as August 15. Authors and producers will be permitted to introduce the films and make running commentaries during their projection.

NEW JERSEY NEURO-PSYCHIATRIC INSTITUTE

The third annual Psychiatric Institute will be held September 21 at the New Jersey Neuro-Psychiatric Institute, Princeton, New Jersey. This year the theme will concentrate on children and their problems, as well as residential centers for treatment of such problems. An invitation may be obtained by writing Dr. Robert S. Garber, Superintendent, New Jersey Neuro-Psychiatric Institute, Box 1,000, Princeton, New Jersey.

ARTHRITIS AND RHEUMATISM FOUNDATION

The Midwest Conference on Rheumatic Diseases, sponsored by the Michigan Chapter of the Arthritis and Rheumatism Foundation and the Michigan Rheumatism Society, will be held at the Henry Ford Hospital in Detroit, Michigan, on October 5. Further information may be obtained from Dr. James L. Lightbody, Medical Director, Arthritis and Rheumatism Foundation, Michigan Chapter, 7338 Woodward Avenue, Detroit, Michigan.

CONGRESS OF NEUROLOGICAL SURGEONS

The Congress of Neurological Surgeons will hold a meeting at the Hotel Statler, Los Angeles, California, on October 27, 28 and 29. Further information may be obtained from Dr. Phillip D. Gordy, 1007 Delaware Avenue, Wilmington, Delaware.

SOCIETY MEETINGS AND CONFERENCES

AUGUST and SEPTEMBER. Beth Israel Hospital Course. Page 509, issue of March 24.
AUGUST 4, 22 and 23. Consultation Clinics for Crippled Children in Massachusetts. Page 1099, issue of June 23.
AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
AUGUST 30 and 31 and SEPTEMBER 1. New England Health Institute. Page 1010, issue of June 9.
SEPTEMBER 12–21, DECEMBER 5–14, 1955, JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
SEPTEMBER 21. Essex North District Medical Society. Notice above.
SEPTEMBER 21. New Jersey Neuro-Psychiatric Institute. Notice above.
SEPTEMBER 30–OCTOBER 1. American Medical Writers' Association. Page 118, issue of July 21.
OCTOBER 1 and 2 and 3–6. American Academy of Pediatrics. Page 118, issue of July 21.
OCTOBER 5. Arthritis and Rheumatism Foundation. Notice above.
OCTOBER 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.
OCTOBER 10–21. New York Academy of Medicine. Graduate Fortnight. Page 84, issue of July 14.
OCTOBER 19 and DECEMBER 14, 1955 and FEBRUARY 15, MARCH 28 and APRIL 18, 1956. Greater Boston Medical Society. Notice above.
OCTOBER 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.
OCTOBER 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.
OCTOBER 26 and NOVEMBER 30, 1955 and JANUARY 25, MARCH 21 and APRIL 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.
OCTOBER 27–29. Congress of Neurological Surgeons. Notice above.
NOVEMBER 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.
NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.
NOVEMBER 7–9. Association of Military Surgeons of the United States. Page 118, issue of July 21.
NOVEMBER 11 and 12. Inter-Society Cytology Council. Page 1056, issue of June 16.
NOVEMBER 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.
NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.
NOVEMBER 28–DECEMBER 2. Interim Session of the American Medical Association, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, AUGUST 11

THURSDAY, AUGUST 11
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

(Concluded on page xviii)

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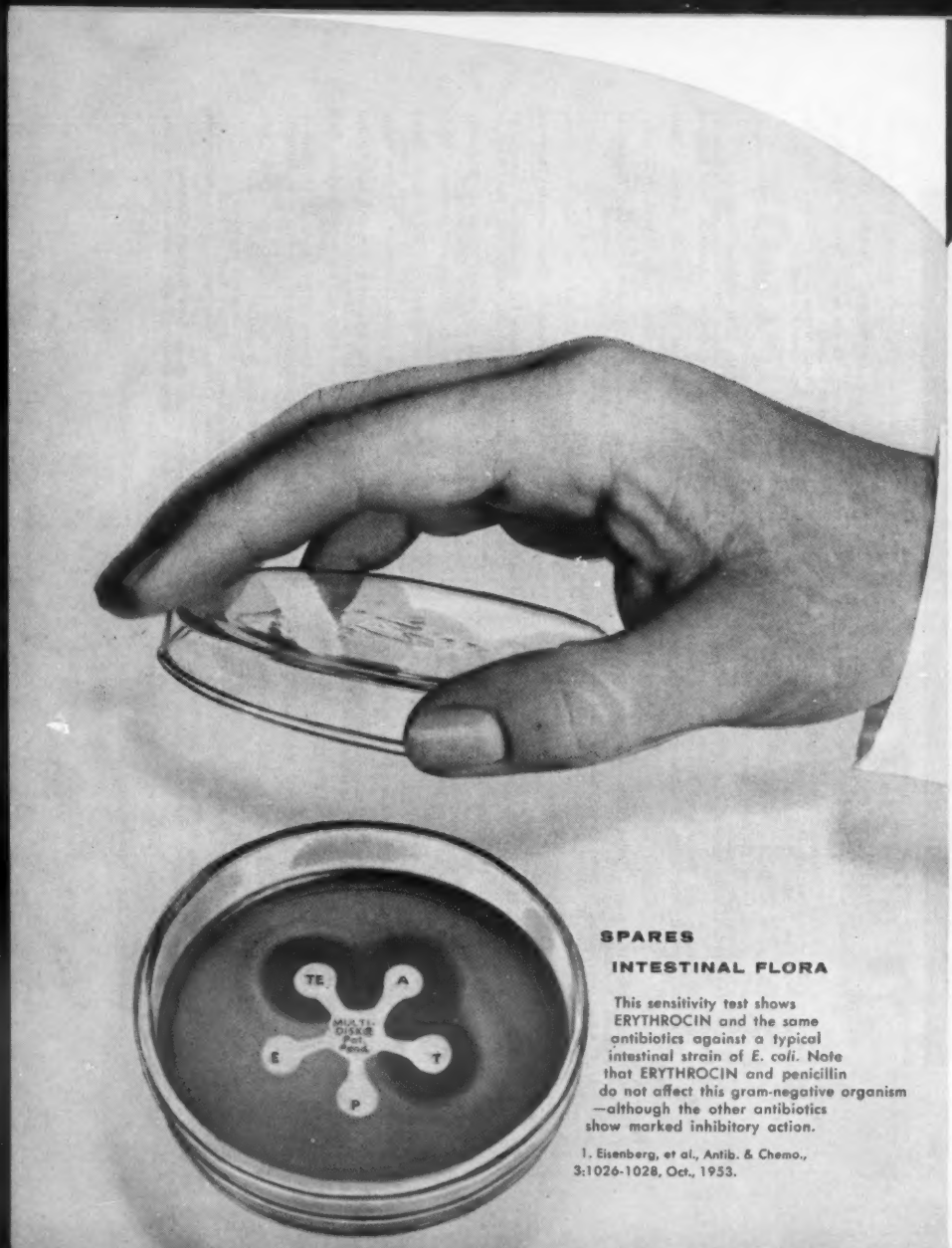

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1. Eisenberg, et al., Antib. & Chemo., 3:1026-1028, Oct., 1953.

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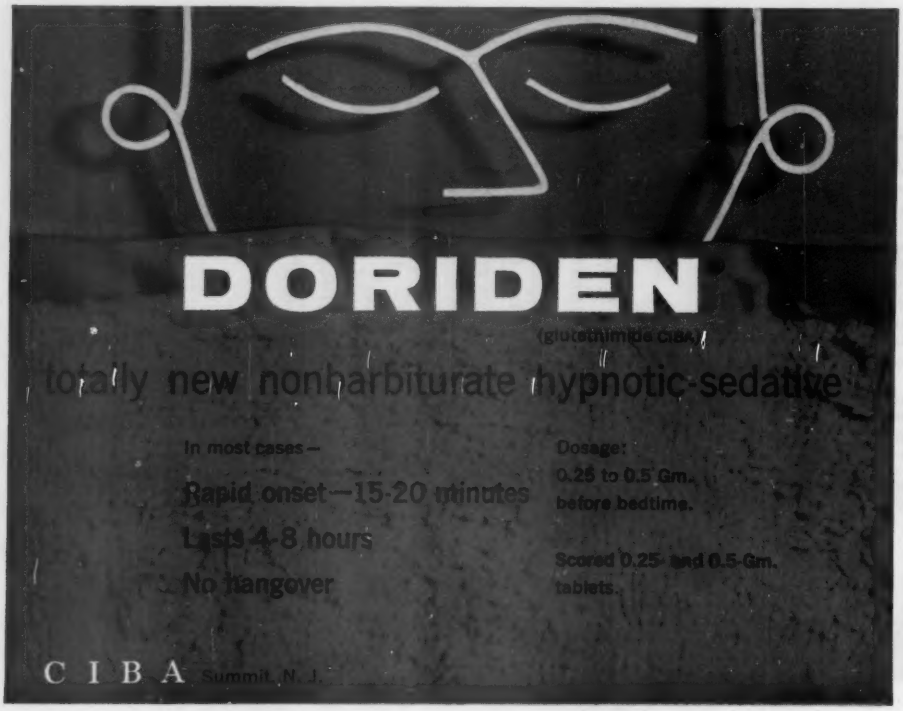

(Concluded from page 208)

11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Thoracic Conference. Ventilatory Studies before and after Pulmonary Resection. Dr. Warren J. Taylor. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, AUGUST 12
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, AUGUST 13
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, AUGUST 15
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.

TUESDAY, AUGUST 16
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, AUGUST 17
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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1. Weinberg, Arthur and Werner, W. E. F.: Bonadoxin, a new effective oral therapy for hyperemesis gravidarum. Am. Pract. and Dig. of Treatment. In press. 2. Personal communication. 3. Berenson, F.: Bonadoxin: oral therapy for nausea and vomiting of pregnancy. In press.

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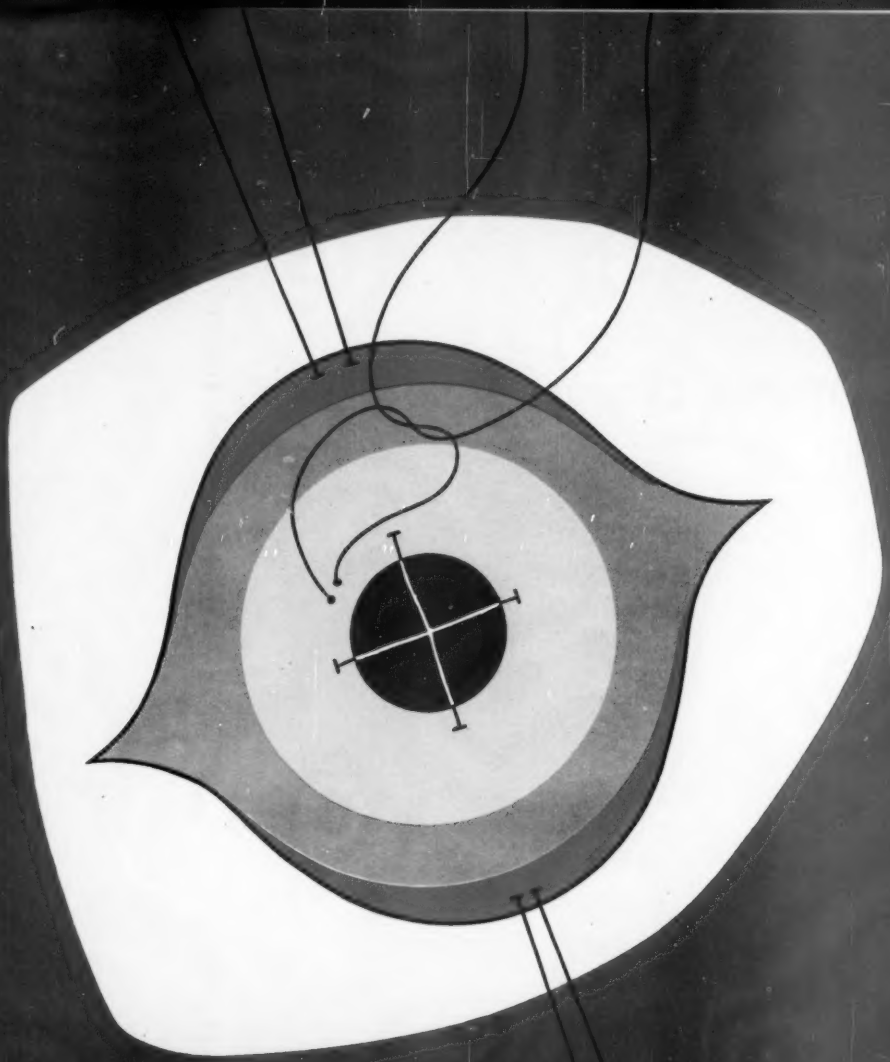

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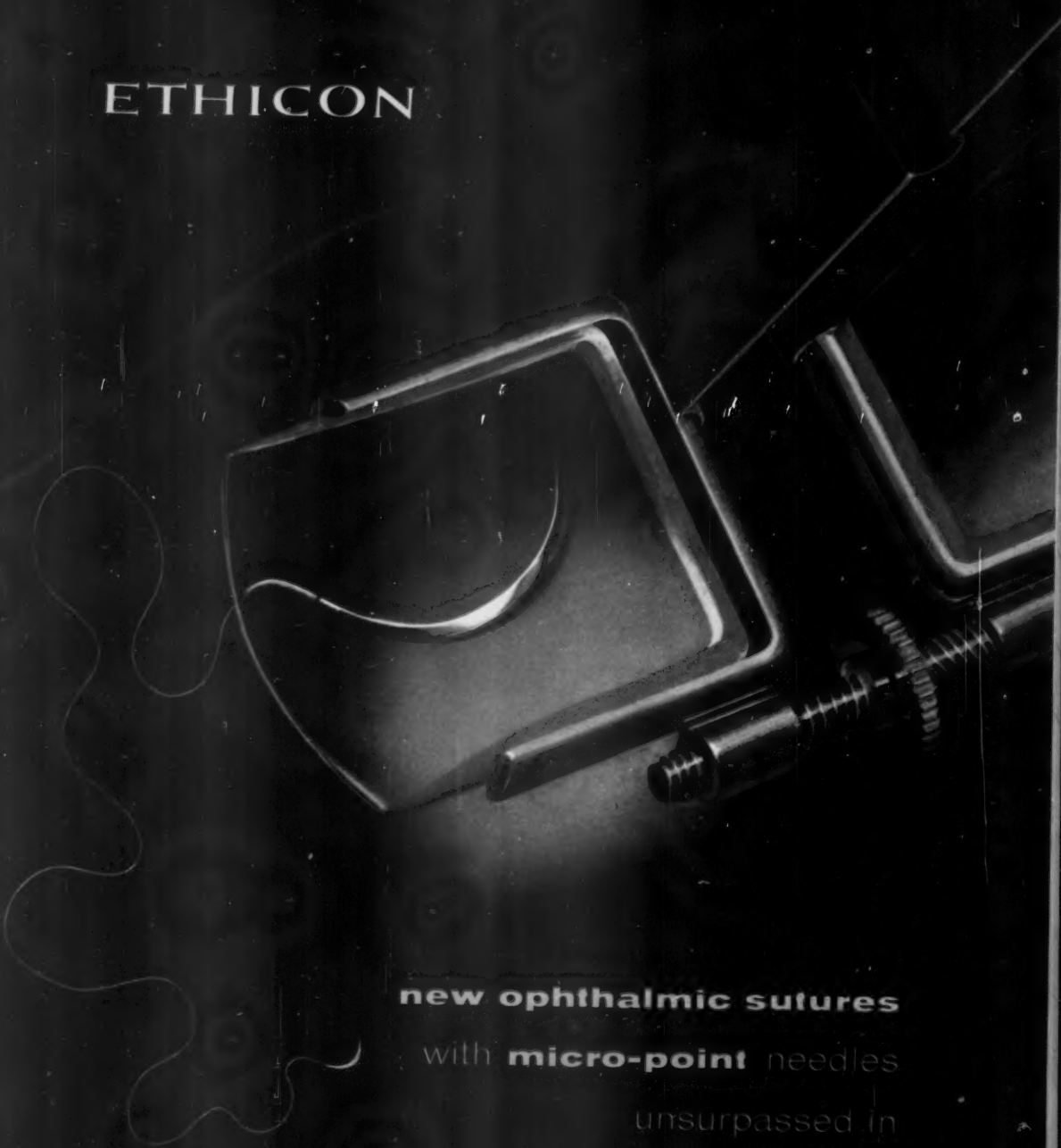

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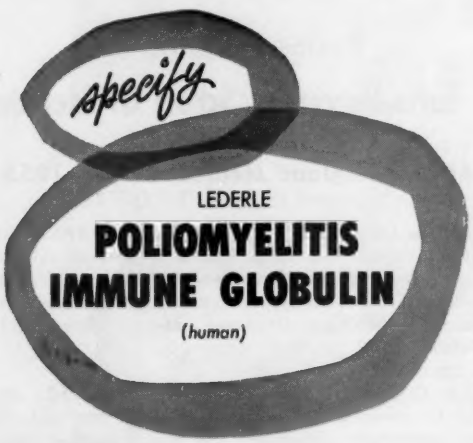

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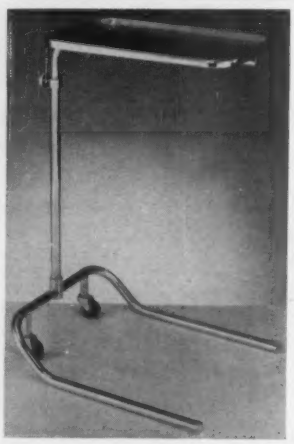

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